Non-Injectable Naloxone for the Prevention of Opioid Overdose Deaths

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NON-INJECTABLE NALOXONE FOR THE PREVENTION OF OPIOID OVERDOSE DEATHS

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This is to certify that

Dr Rebecca Silvia McDonald

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Principal
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Abstract

Background and Aims: Naloxone is the standard treatment for reversal of opioid overdoses. Due to risk of needle-stick injury, licensed injectable naloxone products are not well suited for layperson administration or take-home naloxone distribution. The aims of this thesis are threefold: Aim 1) assess the effectiveness and limitations of take-home naloxone provision (any naloxone formulation); Aim 2) compare the pharmacokinetic profiles of non-injectable naloxone formulations; Aim 3) identify non-injectable formulations that provide early naloxone exposure similar to a 0.4mg intramuscular dose.

Methods: Primary and secondary data analyses were conducted in two stages. The first stage involved evidence syntheses (including two systematic reviews), with secondary data retrieval from the peer-reviewed literature and international patent applications. The second stage involved pharmacokinetic data analysis of two clinical trials (n=12 and 38 healthy volunteers; open-label randomized cross-over design) of concentrated intranasal naloxone formulations (1mg/0.1mL–16mg/0.4mL range).

Results: *Re Aim 1:* Take-home naloxone meets the Bradford Hill criteria. The intervention is effective at reducing opioid overdose mortality and has a low rate of adverse events.

Re Aim 2: Improvised nasal kits using non-concentrated spray (1mg/ml per nostril) have low bioavailability of $F_{IM} \leq 10\%$ (relative to intramuscular administration). Concentrated intranasal spray (≥10mg/ml; administered as ≤0.2mL per nostril) has good bioavailability of $F_{IM} = 26\text{-}57\%$.

Re Aim 3: Relative to the 0.4mg intramuscular reference, a 2mg/0.1mL nasal spray provided equal naloxone exposure in the first 10-minutes post-dosing and then exceeded blood levels for two hours.

Conclusions: Take-home naloxone distribution to opioid users should be introduced as standard of care for the community-based prevention of overdose-related deaths and injury. In the presence of licensed alternatives, continued off-label use of improvised nasal kits is not justified. If approved by relevant regulatory agencies, the 2mg/0.1mL naloxone nasal spray could offer greater acceptability and suitability for take-home naloxone provision.

Table of Contents

Table of Figures

Table of Tables

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During the past three years, I have had the privilege to work with and to learn from my co-authors based here in the UK, in the US, and in Norway, whom I would like to thank for making this multidisciplinary body of work possible. I have also benefited enormously from the interactive environment at the Addictions Department and would like to thank my colleagues, especially Basak Tas for her friendship as well as Drs. Anna Williams, Charlotte Tompkins, Jo Neale, and Kim Donoghue for being sources of motivation and inspiration.

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Finally, I would like to thank my PhD examiners Professor Matthew Hickman and Professor Roy Robertson for reviewing and examining this thesis.

Abbreviations

Abbreviation	Meaning
AIDS	Acquired Immune Deficiency Syndrome
AUC	Area Under The Curve
Cmax	Peak plasma concentration
ED	Emergency Department
F%	Absolute bioavailability (relative to intravenous)
F_{IM}%	Relative bioavailability (relative to intramuscular)
FDA	Food And Drug Administration
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IM	Intramuscular
IN	Intranasal
IV	Intravenous
SL	Sublingual
THN	Take-Home Naloxone
Tmax	Time to peak concentration

Preface

In 1960, Dr. Jack Fishman was the first person to synthesize the naloxone compound. In 2006, his son Jonathan died of a heroin overdose in front of a Miami hospital, where his dealers had reportedly left him (Fishman, 2016). Perhaps like few others, the case of Dr. Fishman's son illustrates that "[m]ost people who die from an overdose do so before reaching hospital" (ACMD, 2000). This highlights the urgent need for technology transfer of naloxone from the Emergency Department (ED) into the community as well as the largely unexploited potential for user-friendly, non-injectable naloxone products that can facilitate bystander intervention.

My interest for this PhD project developed during my previous role as Senior Research Assistant at the National Center on Addiction and Substance Abuse in New York. Between 2010 and 2013, I was involved in a number of projects that aimed to improve treatment access for individuals with substance use disorders in the Bronx and other underserved communities in New York and New Jersey, including the evaluation of a mobile opioid substitution treatment program for homeless and uninsured users. Working together with providers across both states, I became acutely aware of the growing concern of opioid overdose deaths. I was thus immensely grateful for the opportunity of a PhD project that tackled what I consider to be one of the most pressing current public health issues. I began my PhD studies in October 2013, at a time when research interest in naloxone was intensifying (see Figure 1). This allowed me to publish the six first-authored papers which I incorporate in this thesis.

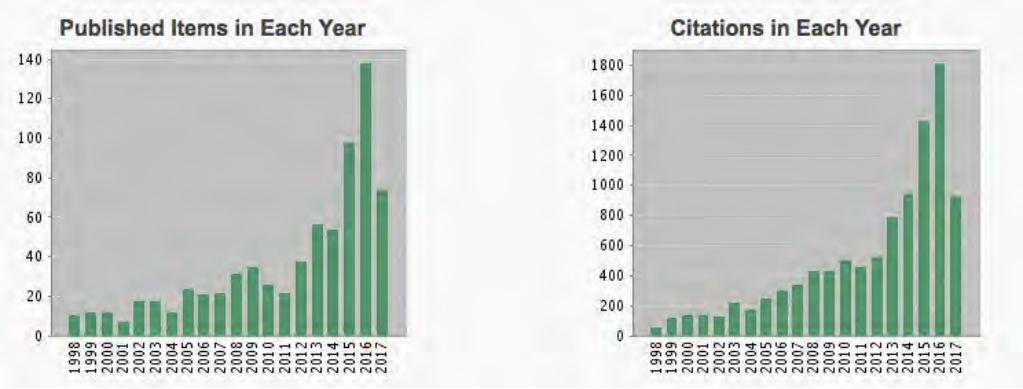

Figure 1 Web of Science citation report for "naloxone AND overdose" (Jan 1998 - May 2017)[1]

[1] Source: Web of Science

However, the rapid increase in research activity also mirrors the escalating opioid crisis in the United States (US) and, to a lesser extent, in the United Kingdom (UK). The prevalence rates of opioid overdose mortality show similar upwards trends in both countries, though the affected populations differ, with a higher proportion of women dying from prescription opioid overdose in the US (see Figure 2 & Figure 3).

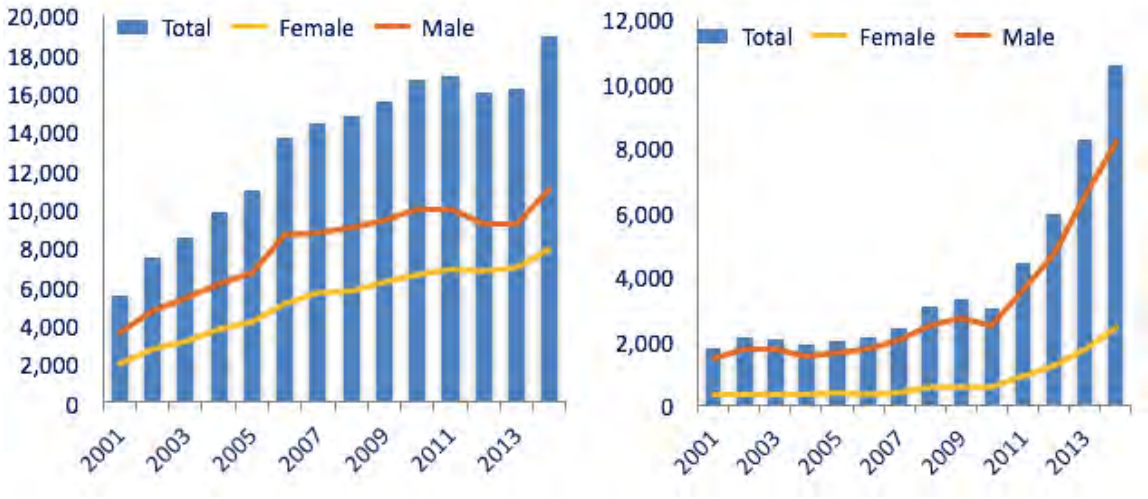

Figure 2 US overdose deaths (2001-14) from prescription opioids (left) and heroin (right)[2]

US overdose fatalities began to rise from the mid-1990s onwards, spurred by a significant increase in prescription opioid abuse (Compton & Volkow, 2006; Paulozzi & Ryan, 2006). Between 1999 and 2010, there was a greater than fourfold increase in overdose deaths from prescription opioids (Volkow, Frieden, Hyde, & Cha, 2014), paralleled by increased prescribing of these medications for the treatment of pain (SAMHSA, 2013) and facilitated by new access through online pharmacies (Jena & Goldman, 2011). Accounting for 16,651 deaths in 2010, prescription opioid overdose fatalities surpassed the number of overdose deaths from heroin and cocaine combined (CDC, 2012a; Volkow et al., 2014). However, more recent evidence suggests an overlapping more acute epidemic of heroin with potential transition toward heroin use as of the mid-2000s, with nationwide hospital data (Unick, Rosenblum, Mars, & Ciccarone, 2013) showing a 44% increase in heroin overdose admissions between 2005 and 2009. The US opioid epidemic has led to a demographic shift in heroin users, from urban minority populations to predominantly white suburban and rural men and women (Cicero,

[2] Source: National Center for Health Statistics (2014)

Ellis, Surratt, & Kurtz, 2014). Overdose mortality rates (any substance) have increased among men and women of non-Hispanic white and black ethnicity (CDC, 2016b). A total of 33,091 opioid overdose deaths were recorded in the US in 2015 (CDC, 2016b).

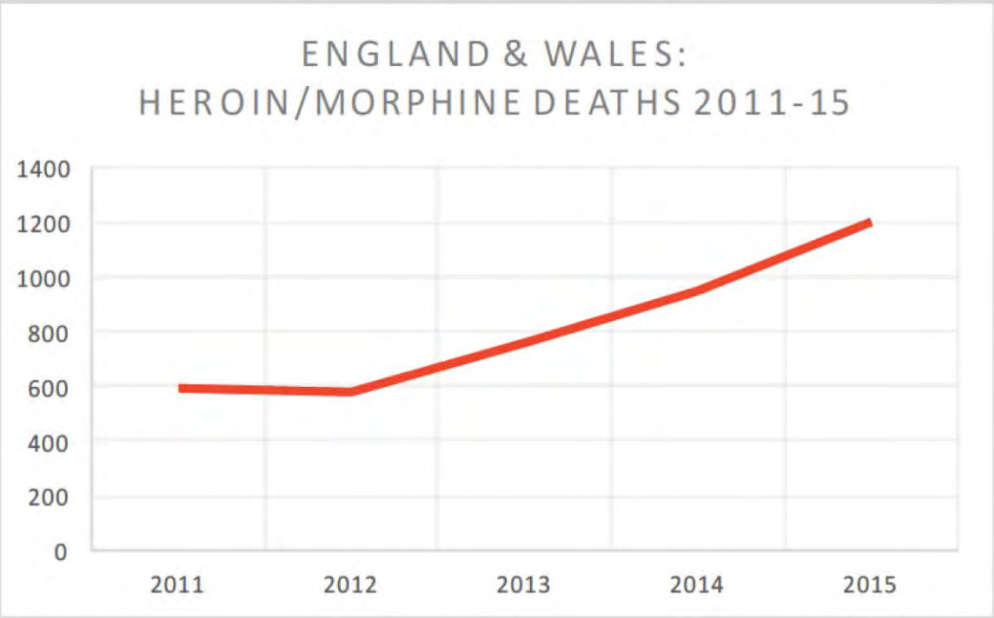

Figure 3 Heroin and morphine deaths in England and Wales (2011-15)[3]

In the UK, latest numbers reveal that heroin and morphine accounted for 1,201 deaths in England and Wales in 2015, reflecting a 102% 5-year increase since 2011 (ONS, 2016). Similarly, a 68% increase in heroin and morphine deaths has been recorded for Scotland, with 349 deaths in 2015 (up from 207 in 2011) (NRS, 2016). Heroin and morphine are main contributors to drug-related deaths in the UK (PHE, 2017), despite representing only a small proportion of the use of illicit drugs. For example, prevalence rates among the general population (adults aged 16-59) were reported to be 0.1% for heroin (past-year use), relative to 1.9% and 6.4% for cocaine and cannabis, respectively (Home Office, 2013). Opiate overdose accounts for nearly half of all deaths among heroin injectors, exceeding human immunodeficiency virus (HIV) and other disease-related deaths (Hickman et al., 2003). According to public estimates, nearly three quarters (74%) of current drug overdose deaths in the UK occur in men (PHE, 2017). Moreover, the proportion of older heroin users, aged ≥40 years, of any drug treatment

[3] Source: ONS (2016)

status has been steadily increasing (PHE, 2017), and their risk of overdose death is presumed to be increased due to physical comorbidity and complex health needs.

From 2000 onwards, the possibly greater suitability of a non-injectable form of naloxone was occasionally mooted (Strang, 1999), and improvised nasal naloxone kits began to be constructed in some parts of the world, using existing injectable formulations and their administration through simple attachment of an atomizer spray device. However, no approved nasal naloxone products existed, and no data were available on the extent of absorption of naloxone from these improvised nasal kits, apart from a concerning report of extremely poor bioavailability reported from one investigative group (Dowling, Isbister, Kirkpatrick, Naidoo, & Graudins, 2008).

An important step forward occurred when, in April 2012, the US Food and Drug Administration (FDA) and partner agencies convened a public meeting to encourage the development of non-injectable naloxone formulations.

The overarching research objective of my PhD project has thus been to study novel injection-free naloxone formulations with potential to deliver rapid overdose reversal. In order to operationalize this goal, I have developed the following three aims:

- Aim 1: Assess the effectiveness and limitations of take-home naloxone provision (any naloxone formulation)
- Aim 2: Compare the pharmacokinetic profiles of non-injectable naloxone formulations
- Aim 3: Identify non-injectable formulations that provide early naloxone exposure similar to a 0.4mg intramuscular dose

To address these aims, I have applied a two-stage test strategy. The first stage involves evidence syntheses (**Chapters 2-6**), including secondary data retrieval from the peer-reviewed literature and international patent applications. The second stage (**Chapters 7-8**) involves pharmacokinetic data analysis of clinical trials of naloxone nasal spray in healthy volunteers.

The structure of the thesis is as follows: In the two opening chapters, I present a review of the literature that follows the journey of the naloxone from its first synthesis in a Long Island laboratory in 1960 into emergency rooms and ambulances (**Chapter 1**) and, from 1996 onwards, into the community through provision of take-home naloxone to opioid users and family members (**Chapter 2**). I describe the pharmacological properties of the antidote and address current and past limitations of take-home naloxone implementation (Aim 1) as backdrop for my empirical work in the following chapters.

In **Chapter 3**, I conduct a systematic review of the effectiveness of take-home naloxone programs (Aim 1). The rationale is straightforward: If take-home naloxone provision has no impact on opioid overdose mortality, then there is little reason to invest in the study and development of new non-injectable formulations. If, however, take-home naloxone is effective and safe, then reformulation of naloxone needs to be explored so as to facilitate and expand community-based access to the antidote.

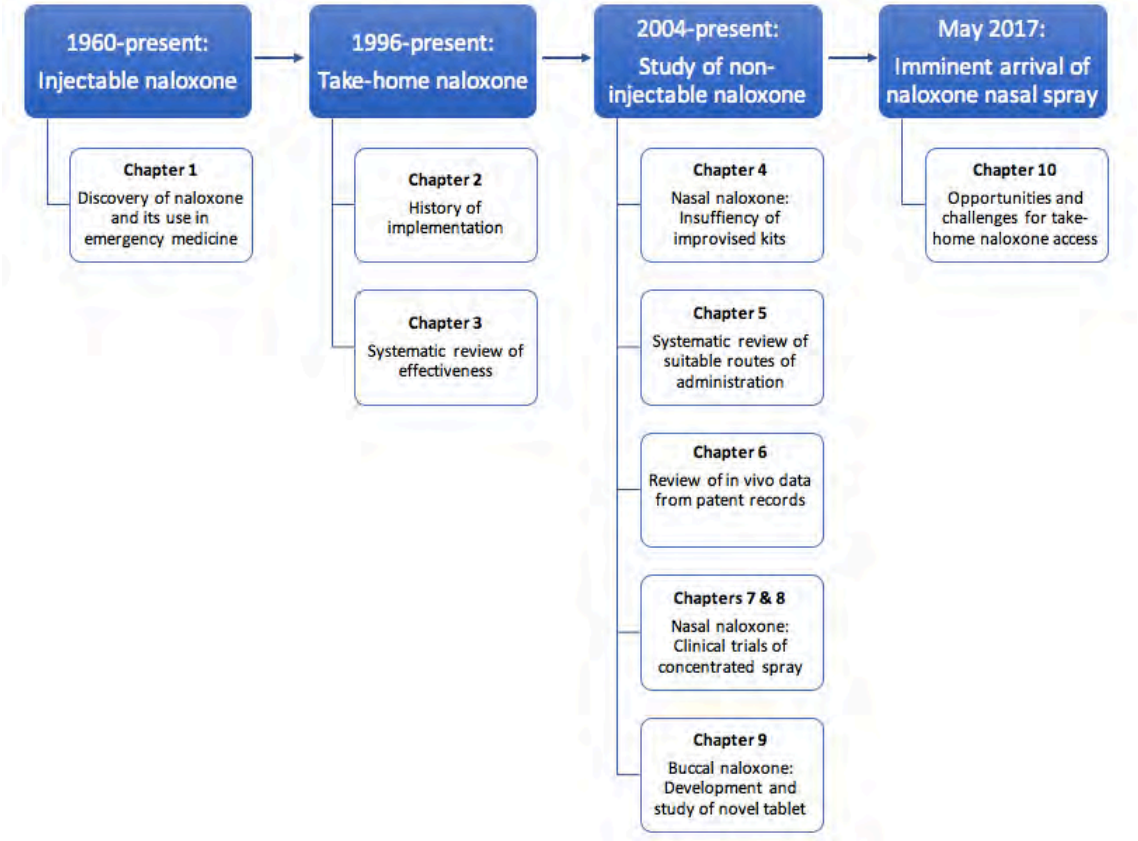

Figure 4 Thesis outline

In **Chapter 4**, I then assess the evidence base for existing improvised nasal naloxone kits, which are already in use in the US and parts of Scandinavia. Having established that take-home naloxone is effective (Aim 1) but that the pharmacokinetic profile and safety of the improvised kits are uncertain (Aim 2), I conclude that study of novel non-injectable formulations is needed.

I thus proceed to the next stage of testing in **Chapter 5** where I conduct a second systematic review by applying the FDA's regulatory criteria for naloxone products to all

routes of drug administration listed by the FDA (n=112) in order to identify injection-free routes with potential suitability for naloxone delivery in the overdose emergency.

Given the limited data availability in the peer-reviewed literature, I then extend my search for human pharmacokinetic data for non-injectable naloxone formulations to industry sources through exploratory review of international patent applications – which I report in **Chapter 6**. Integration of the evidence reported in the patent documents allows me to determine the key characteristics for a naloxone nasal spray for treatment of opioid overdose, with concentrated formulations and low volumes of administration being essential for efficient nasal mucosal absorption (Aim 2).

Working together with industry, I then move towards the development and study of new purpose-made naloxone nasal spray in this second part of my PhD project. I analyze an archived dataset from a 2004 clinical trial (n=12; cross-over design), of high-dose (8mg, 16mg) naloxone nasal spray in **Chapter 7** in order to inform target doses (1mg, 2mg, 4mg) for the design of the new clinical trial of concentrated naloxone nasal spray in healthy volunteers (n=38; cross-over design) – undertaken specifically for the purpose of potential future application as emergency medicine for opioid overdose reversal by non-medical personnel. I present my pharmacokinetic data analysis of the new clinical trial in **Chapter 8**, identifying a 2mg/0.1mL intranasal dose as providing equal early naloxone exposure as a 0.4 intramuscular injection (Aim 3).

In **Chapter 9**, I introduce a more recent alternative to injectable naloxone that, with colleagues at the Institute of Pharmaceutical Science, my supervisors, and I have jointly developed: an instant-dissolving buccal naloxone tablet. I attach a copy of the patent, which lists me as co-inventor, in Appendix C.

In **Chapter 10,** I integrate the findings from Chapters 2 to 9 and address their implications for clinical practice, policy, and future research.

A nasal naloxone spray product is now licensed in North America, and the arrival of a first non-injectable naloxone product in Europe is anticipated for late 2017 or early 2018.

This thesis incorporates my six first-authored publications in the leading specialty journals, including *Addiction*, *Drug and Alcohol Dependence*, and *Drug and Alcohol Review* which report the work which has comprised much of my PhD studies. I include copies of these publications in Appendix B. For convenience, I provide the references of the publications along with the study aims by thesis chapter in Table 1. A graphic outline of the thesis is provided in Figure 4.

Table 1 Aims and first-authored publications by thesis chapter

Chapter	Aims	Publication
Ch. 1 **"**The Discovery of Naloxone"	• Describe the discovery of naloxone and its use in clinical practice • Describe the pharmacokinetics and pharmacodynamics of naloxone	--
Ch. 2 "Twenty Years of Take-home Naloxone"	• Identify key events in the emergence and evolution of take-home naloxone	McDonald, R., Campbell, N.D, & Strang, J (in press). Twenty years of take-home naloxone for the prevention of overdose deaths from heroin and other opioids – conception and maturation. *Drug and Alcohol Dependence.*
Ch. 3 "Bradford Hill Analysis of Take-home Naloxone"	• Describe the impact of take-home naloxone provision on overdose-related mortality in opioid users • Assess the safety of take-home naloxone provision by quantifying adverse events associated with naloxone administration	McDonald, R., & Strang, J. (2016). Are take-home naloxone programmes effective? Systematic review utilizing application of the Bradford Hill criteria. *Addiction*, *111*(7), 1177-1187.
Ch. 4 "The Insufficiency of Improvised Nasal Naloxone Kits"	• Assess the provision of improvised nasal naloxone in clinical practice • Examine published evidence of pharmacokinetics and effectiveness of naloxone by nasal administration relative to injection	Strang, J.*, McDonald, R.*, Tas, B., & Day, E. (2016). (* joint first authors) Clinical provision of improvised nasal naloxone without experimental testing and without regulatory approval: imaginative shortcut or dangerous bypass of essential safety procedures? *Addiction, 114*(04), 574-82.
Ch. 5 "Non-injectable Routes of Naloxone Administration"	• Identify candidate routes of injection-free naloxone administration potentially suitable for emergency overdose reversal • Consider pathways for developing and evaluating novel naloxone formulations	Strang, J.*, McDonald, R.*, Alqurshi, A., Royall, P., Taylor, D., & Forbes, B. (2016). (* joint first authors) Naloxone without the needle− systematic review of candidate routes for non-injectable naloxone for opioid overdose reversal. *Drug and Alcohol Dependence*, *163*, 16-23.

Chapter	Aims	Publication
Ch. 6 "Patent Applications for Non-Injectable Naloxone"	• Trace the concept and product development by route of administration • Describe the non-injectable naloxone formulations for which human in vivo data are available • Compare human pharmacokinetic data reported in the patent applications	McDonald, R.*, Glende, Ø.D.*, Dale, O, & Strang, J. (in press). (* joint first authors) International patent applications for non-injectable naloxone for opioid overdose reversal: Exploratory search and retrieve analysis of the PatentScope database. *Drug and Alcohol Review.*
Ch. 7 "Early Study of Concentrated Nasal Naloxone"	• Describe the pharmacokinetic properties of two high-concentration intranasal naloxone formulations • Assess naloxone absorption in the clinically-relevant period of the first 30 minutes post-administration • Assess dose proportionality of the two intranasal naloxone formulations	Mundin, G.*, McDonald, R.*, Smith, K., Harris, S., & Strang, J. (2017). (* joint first authors) Pharmacokinetics of concentrated naloxone nasal spray over first 30 minutes post-dosing: analysis of suitability for opioid overdose reversal. *Addiction*. DOI: 10.1111/add.13849
Ch. 8 "New Study of Concentrated Nasal Naloxone"	• Assess the pharmacokinetic profile of intranasal naloxone • Compare its early partial systemic exposure to the intramuscular reference. • Determine intranasal bioavailability	(manuscript under review)
Ch. 9 "Beyond Nasal: The Exploration of Buccal Naloxone"	• Develop a buccal tablet that contains a clinically relevant naloxone dose and dissolves instantly (e.g. ≤ 30 s) • Test the stability and dissolution of the tablet in vitro • Test the pharmacokinetics of buccal naloxone administration in humans	--
Ch. 10 "Discussion"	• Integrate findings • Discuss implications for clinical practice, policy, future research	--

Chapter 1 The Discovery of Naloxone

Preface

In this opening chapter, I present a review of the remarkable properties of naloxone and its application for the reversal of opioid overdose.

Naloxone is a potent antidote. Antidotes are defined as “therapeutic substance[s] used to counteract the toxic action(s) of a specified xenobiotic” (WHO/CEC, 1993). The prompt administration of antidotes can reduce patient morbidity and mortality as well as the burden placed on healthcare systems, and their availability is essential, particularly in areas or countries with limited access to emergency medical care. Examples of other emergency medicines include glucagon (for severe acute hypoglycemia in treated diabetes) and flumazenil (for benzodiazepine overdose). While there is substantial variation in the efficacy of antidotes in general, the clinical effect of naloxone is considered “both rapid and dramatic” (WHO/CEC, 1993).

The first part of this chapter describes the discovery of naloxone and its pharmacokinetics and explains why, almost 60 years after its original synthesis, naloxone remains the opioid antagonist of choice for the treatment of acute opioid overdose.

The second part summarizes how heroin and other opioids impact the respiratory system and reviews the pharmacodynamics of naloxone, i.e. how naloxone reverses respiratory depression during opioid overdose.

A third and final part describes the shift from intravenous to intramuscular naloxone administration that occurred in ambulance care in the 1990s and effectively set the scene for the introduction of take-home naloxone programs which are reviewed in Chapters 2 and 3.

1.1 What is Naloxone?

Naloxone (N-allylnoroxymorphone, N-allyl-14-hydroxydihydro-nor-morphinone; see Figure 5) is an antidote that counters the effects of heroin and other opioids. It can reverse any potentially life-threatening respiratory depression that the opioid agonists have caused by blocking their ability to occupy receptor sites and displacing opioids which are already occupying receptors. Naloxone is a specific opioid antagonist (Martin, 1976) with affinity for all three opioid receptors (mu > kappa ≥ delta) (Rang, Dale, Ritter, Flower, & Henderson, 2012). It is a semi-synthetic antagonist that is made from thebaine, an alkaloid component that is extracted from the opium poppy plant and has no direct therapeutic uses itself (EMCDDA, 2016a). At least three synthetic routes have been reported to produce naloxone (Hassan, Mohamed, & Mian, 1985). The main clinical use of naloxone is to treat respiratory depression caused by opioid overdose (Rang et al., 2012). Naloxone has no abuse potential due to lack of euphoriant effect (Brunton, Chabner, & Knollman, 2010), and it is associated with only a small rate of adverse effects (Buajordet, Næss, Jacobsen, & Brørs, 2004).

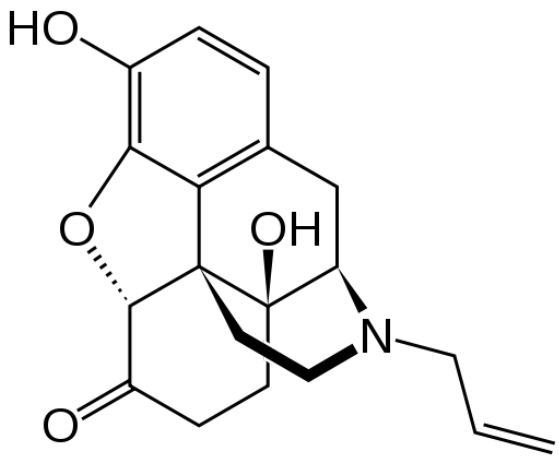

Figure 5 The molecular structure of naloxone[4]

1.1.1 The early development of naloxone

Naloxone was first synthesized in 1960 by Dr. Jack Fishman (see Figure 6). Born Jacob Fiszman in Krakow, Poland, in 1930, Dr. Fishman had fled Nazi occupation with his family at 8 years of age and, after spending his youth in Shanghai, China, immigrated to

[4] Source: EMCDDA (2016a)

the US in 1948 (The New York Times, 2013). He trained in chemistry in New York in the late 1940s and early 1950s, and his subsequent PhD thesis at Wayne State University (Detroit, Michigan) involved steroid and alkaloid research (Garfield, 1983; Yardley, 2013).

Figure 6 Dr. Jack Fishman (1930-2013)[5]

By the late 1950s, Dr. Fishman held a position in steroid research at the Sloan Kettering Institute for Cancer Research, New York, and was also working on alkaloid opioid research in the private laboratory of Dr. Mozes J. Lewenstein. One of the goals of his research at Dr. Lewenstein's laboratory was to find a potent opioid antagonist without major adverse side effects (Garfield, 1983). Among other compounds, Dr. Fishman synthesized naloxone in 1960 (see Table 2), which would prove to be the solution to his search for the specified antagonist.

It is interesting to note that the original synthesis of naloxone was first disclosed in a patent rather than as journal article (see also Chapter 6).

Drs. Lewenstein and Fishman submitted a patent application in March 1961 stating that naloxone was a "more potent antagonist to the respiratory depressive effects of potent analgesics than the antagonists hitherto known" (Garfield, 1983). The patent was issued in May 1966 (Lewenstein & Fishman, 1966).

[5] Source: The New York Times

Outside of his private research laboratory, Dr. Lewenstein headed the Narcotics Division at Endo Laboratories (New York), and he licensed naloxone to Endo for evaluation (Garfield, 1983). At Endo, the director of biological laboratories, Dr. Harold Blumberg, who was a biochemist and toxicologist by training, soon started testing the new compound's properties in animals. In a 1961 abstract in Federation Proceedings, Dr. Blumberg and colleagues introduced naloxone as a "potent, rapid-acting, and relatively pure narcotic antagonist", which counteracted the effects of a range of opioid agonists, including morphine and methadone (Blumberg, Dayton, George, & Rapaport, 1961).

The first full-length journal article on naloxone was published by the Japanese pharmaceutical company Sankyo in 1962 (Minakami et al., 1962). While it is not possible to delineate what share Sankyo had in the early investigation of naloxone, the company's impact on future naloxone research was limited: Over the course of the next two decades, over 100 patents and journal articles cited the 1961 patent and abstract by Drs. Fishman, Blumberg, and Lewenstein, acknowledging their role as the early developers of naloxone, whereas the 1962 Sankyo paper was only cited once (Garfield, 1983).

Following their pioneering work around naloxone in 1960/61, Dr. Fishman carried on his work at Dr. Lewenstein's laboratory and synthesized over a dozen related opioid agonists and antagonists. He also explored ways to prolong the duration of action of naloxone (Fishman, Hahn, & Norton, 1975; Heilman, Hahn, & Fishman, 1975; Linder & Fishman, 1973) and studied its disposition (i.e. absorption, distribution, metabolism, and excretion) in humans (Fishman et al., 1975; Fishman, Roffwarg, & Hellman, 1973). Meanwhile, Dr. Blumberg continued to publish on naloxone and on two closely related opioid compounds, the agonist-antagonist nalbuphine and the longer-acting antagonist naltrexone (half-life about 10 hours) (Rang et al., 2012). Dr. Blumberg applied for regulatory review of naltrexone, which received its original FDA approval for opioid addiction in 1984. From 1974 onwards, Dr. Blumberg served as a consultant to the U.S. National Institute on Drug Abuse (NIDA).

In 1982, Drs. Fishman and Blumberg received the prestigious John Scott Award in recognition of their "useful invention", i.e. the original synthesis of naloxone by Dr. Fishman and its significant biological investigation by Dr. Blumberg. To quote the speech that Dr. Eugene Garfield, a member of the John Scott Award Advisory Committee, delivered at the award ceremony (Garfield, 1983): "While no one at the time could have recognized how important naloxone would become, the story reveals once again the way in which basic research works to the advantage of mankind".

1.1.2 The predecessors of naloxone and more recent alternatives

Although not the first opioid antagonist, naloxone is regarded as the first pure opioid antagonist free of agonist effects (Martin, 1976; Rang et al., 2012). As such, naloxone constitutes a safer and more powerful opioid antagonist with fewer side effects than its predecessors, nalodeine and nalorphine.

Both nalodeine and nalorphine were only partial antagonists, acting as agonists of the kappa-opioid receptor. Nalodeine (N-allyl-norcodeine) was discovered in 1915 as the first-ever opioid antagonist – but it was never marketed. Nalorphine (N-allyl-normorphine; trade name: Nalline), a morphine derivative, entered clinical practice in 1954 and was commonly used as an antidote to reverse opioid overdose and as opioid challenge test ("Nalline test") (Terry & Braumoeller, 1956; Wikler, Fraser, & Isbell, 1953). The latter involves injecting an individual with nalorphine to test if its antagonistic effects precipitate withdrawal symptoms, indicating the presence of opioids and potential opioid dependence of the individual (Grupp, 1970). While nalorphine effectively reversed opioid overdoses in most cases, its activation of the kappa-opioid receptor could produce strong side effects, including hallucinations and, paradoxically, reduced respiration (Garfield, 1983).

A breakthrough which established naloxone as the superior opioid antagonist was Dr. Blumberg's study (1966) of naloxone's action against the analgesic (i.e. agonist) activity of nalorphine. Naloxone reversed the agonist activity of nalorphine while showing no agonist activity of its own.

In the early 1970s, nalmefene, an opioid antagonist related to naltrexone, was developed as a potential alternative to naloxone. Nalmefene exceeded naloxone in its biological half-life (11±5 hours versus 1±0.5 hours) and oral bioavailability. Immediate-release injectable nalmefene (trade name: Revex), manufactured by Baxter Healthcare Corporation, received FDA-approval for opioid overdose reversal in 1995. However, Baxter discontinued Revex in 2008 (FDA, 2008), presumably because Revex was more expensive than naloxone and its sales volume limited accordingly. (In the UK, nalmefene is only licensed, as an oral tablet medication, for the reduction of alcohol consumption in patients with alcohol dependence (NICE, 2014)).

To summarize, naloxone – due to its unique effectiveness and safety profile, paired with its relatively low cost – has been the opioid antagonist of choice since its regulatory approval nearly half a century ago.

1.1.3 Regulatory approval

The US FDA approved naloxone in 1971 as prescription-only medication for intravenous, intramuscular, and subcutaneous administration for reversing the effects of opioids. Naloxone entered clinical practice in Europe in the following years. Injectable naloxone-hydrochloride solution is commercially available in formulations ranging from 0.4mg/mL to 1mg/mL. Initially marketed under the trade name Narcan in the US, injectable naloxone now exists off-patent as a generic medicine.

In 2015, a naloxone nasal spray (4mg/0.1mL) also received FDA approval (see Chapter 4). However, in the remainder of this chapter, "naloxone" refers to naloxone-hydrochloride solution for injection, unless otherwise specified.

1.1.4 Inclusion in the WHO Model List of Essential Medicines

In 1983, naloxone (0.4mg in 1mL-ampoules) was included as specific antidote in the WHO (World Health Organization) Model List of Essential Medicines, which lists "the most efficacious, safe and cost-effective medicines for priority conditions" (WHO, 2011a, 2015). The shelf-life of injectable naloxone is three years in temperate as well as tropical countries, which makes the antidote well suited for global use.

Table 2 Key events in the original development of naloxone

Year	Month	Country	Event
1915			Nalodeine is discovered as the first opioid antagonist
1954			Nalorphine is development and introduced
1960		USA	Naloxone is first synthesized by Dr. Jack Fishman
1961	March	USA	Drs. Jack Fishman and Mozes J. Lewenstein apply for first US patent for naloxone (issued in May 1966)
		USA	Dr. Harold Blumberg and colleagues publish abstract on naloxone in *Federation Proceedings*
1962	March	UK	Sankyo Company Ltd. applies for British patent for naloxone (issued in October 1963)
		Japan	Minakami et al. of Sankyo publish first full-length journal article on naloxone in *Life Sciences*
1966		USA	Blumberg et al. paper demonstrates naloxone's superior safety profile compared to nalorphine
1971		USA	FDA licenses naloxone as prescription-only medication
1983		Int'l	Naloxone is added to the WHO List of Essential Medicines

1.2 Pharmacokinetics

I now describe how the human body handles naloxone, i.e. how the concentration of naloxone in human blood changes over time following dosing. This section only relates to parenteral injection of naloxone. The pharmacokinetics of non-injectable (i.e. nasal, sublingual) naloxone are presented in Chapters 4 to 8.

Dhillon and Gill (2006) define pharmacokinetics as "a mathematical basis to assess the time course of drugs and their effects on the body. It enables the processes [of absorption from the site of administration, distribution within the body, metabolism, and excretion] to be quantified."

The study of pharmacokinetics generally focuses on concentrations of a drug (i.e. naloxone) in blood plasma, which is obtained from intravenous blood samples. The rationale is that "plasma concentrations are assumed usually to bear a clear relation to the concentration of drug in extracellular fluid surrounding cells that express the receptors or other targets with which drug molecules combine" (Rang et al., 2012). To put it simply, blood plasma concentrations of naloxone are representative of naloxone availability at the therapeutic target site, i.e. opioid receptors in the brain.

The pharmacokinetics of naloxone were first studied in the years following its original synthesis in 1960 (see below), but assay methods were not very advanced at the time. Radioimmunoassay (RIA) for naloxone assay was first reported in the 1970s (Berkowitz, Ngai, Hempstead, & Spector, 1975) but was challenging, because availability of the required antibody was limited. Gas-liquid chromatography (GLC) and high-performance liquid-chromatography (HPLC) for naloxone assay followed in the 1980s (Asali, Nation, & Brown, 1983; Meffin & Smith, 1980; Terry, Hisayasu, Kern, & Cohen, 1984), of which HPLC was considered the more reliable method. Modern liquid chromatography-tandem mass spectrometry (LC-MS/MS) method, as used for the chemical analysis of the results presented in Chapters 7 and 8, exceeds these earlier assay methods in sensitivity, as it combines the physical separation capabilities of HPLC with the mass analysis capabilities of mass spectrometry, but has only become widely available since the mid-1990s (Grebe & Singh, 2011).

1.2.1 Absorption

Absorption describes the passage of naloxone from its site of administration into the blood plasma (Rang et al., 2012). Naloxone appears to be readily absorbed after oral administration, but only a small proportion reaches the systemic circulation. In an early

study in healthy volunteers, Fishman et al. found that orally administered radiolabelled naloxone underwent extensive first-pass hepatic metabolism (Fishman et al., 1973). Its low bioavailability (≤ 2%) makes the oral route unreliable for naloxone administration (Smith et al., 2012). For maximum effectiveness, naloxone must consequently be given by a route that bypasses ingestion and first-pass metabolism (Brunton et al., 2010). When given intravenously, naloxone reaches peak plasma concentrations almost immediately. The peak plasma concentration is slightly delayed (at approximately 10-12 minutes) when administered intramuscularly (WHO, 2014), see Figure 7.

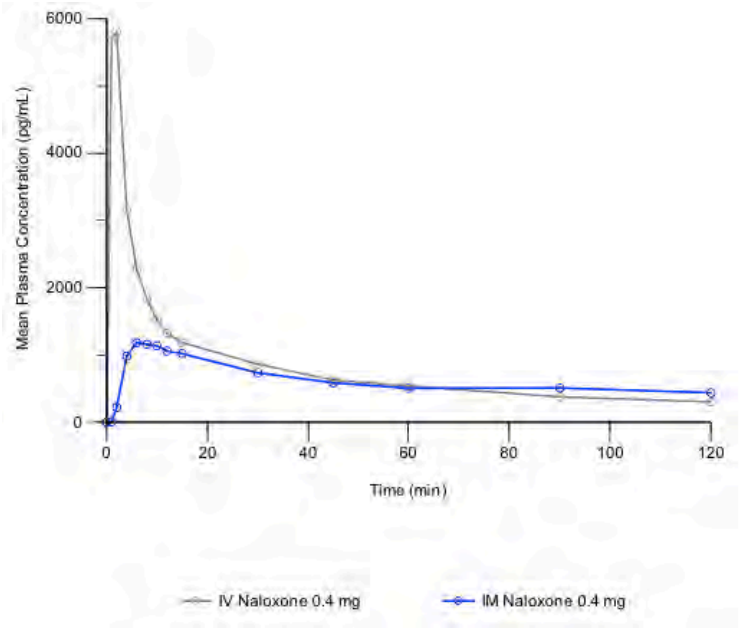

Figure 7 Naloxone plasma concentration from 0.4mg parenteral dose: intravenous (IV) versus intramuscular (IM) administration (see also Chapter 8)

1.2.2 Distribution

Naloxone is highly lipid soluble (Rang et al., 2012). Once absorbed, naloxone is rapidly distributed throughout the body and crosses the blood-brain barrier (NIH, 2007a). In an experimental study in rats, Fishman et al. observed that the distribution of naloxone was not altered by a 25-fold morphine (Fishman et al., 1975). The fact that the distribution of naloxone was not compromised by the presence of opioid agonists lent further support to the unique suitability of naloxone for the reversal of opioid overdose.

1.2.3 Metabolism

When naloxone reaches the liver, it is rapidly metabolized to its two metabolites naloxone-3-glucuronide and 6-alpha-naloxol. While inactive, naloxone-3-glucuronide can be used as a marker when measuring the levels of naloxone in the body (Smith et al., 2008). In a rodent study, naloxone was found to be 65-fold more potent than 6-alpha-

naloxol to precipitate opioid withdrawal (Schulteis, Chiang, & Archer, 2009). 6-alpha-naloxol is thus not considered to be clinically relevant.

The half-life of naloxone (i.e. the time required for the naloxone plasma concentration to be reduced to half) is variable and averages around 1±0.5 hours (NIH, 2007).

1.2.4 Excretion

After an oral or intravenous dose, about 25-40% of naloxone is excreted as metabolites in urine within 6 hours, about 50% in 24 hours, and 60-70% in 72 hours (WHO/CEC, 1993).

1.3 Pharmacodynamics

In the following sections, I describe the pharmacodynamics of naloxone, i.e. how naloxone reverses opioid overdose, after a summary of how opioid overdose leads to respiratory depression.

1.3.1 Opioid-induced respiratory depression

Opioid overdose causes respiratory and central nervous system depression. Understanding the significance of naloxone requires some knowledge of respiratory depression. To review briefly, mu-opioid receptors are the most widespread opioid receptor group in the body and the primary target for many analgesic drugs, but they can also produce adverse effects including respiratory depression (Pasternak, 2006). While normal lung function serves to maintain high concentrations of oxygen and low concentrations of carbon dioxide in body tissues (Levitzky, 2013), consumption of opioids interrupts the feedback loop between the lungs and the respiratory centers in the brain and reduces the respiratory rate. Heroin or opioid metabolites bind to the mu-opioid receptors in the respiratory centers in the brain (see Figure 8). The drug and also active metabolites dampen brain activity in areas associated with inspiration, whereas brain areas associated with expiration are unaffected. This can lead also to hypercapnia (elevated carbon dioxide levels in the blood) as well as to hypoxemia (low levels of blood oxygen).

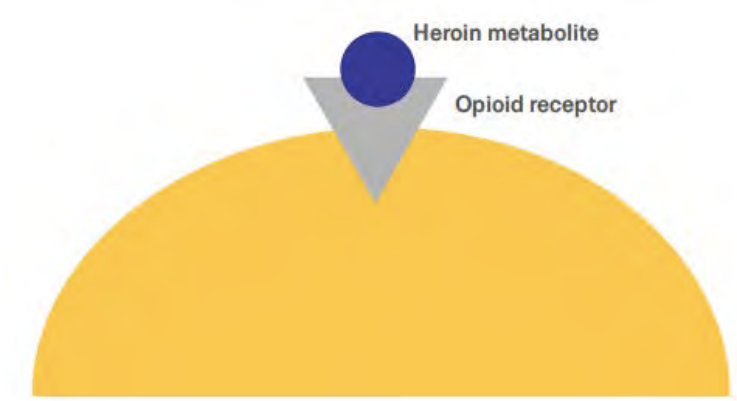

Figure 8 Heroin metabolite attaches to a mu-opioid receptor (triangle)[6]

The effect of opioid consumption on oxygen levels is illustrated by Figure 9, which shows a dramatic drop in blood oxygen levels within ten minutes of intravenous heroin injection.

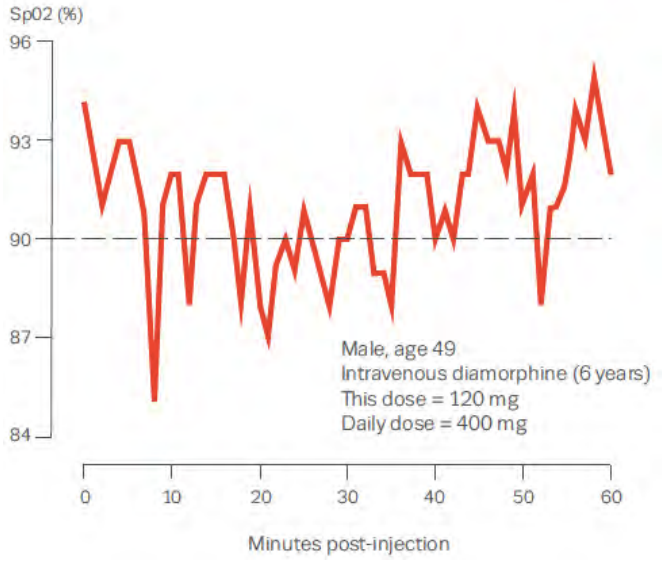

Figure 9 Oxygen saturation levels after intravenous opioid injection[7][8]

[6] Source: EMCDDA (2016a)

[7] Source: *idem*

[8] SpO_2: peripheral capillary oxygen saturation

During overdose, the respiratory rate drops and becomes irregular, with temporary cessation of breathing (“apnea”) (Leino, Mildh, Lertola, Seppaelae, & Kirvelä, 1999). If the respiratory rate is reduced for an extended time, breathing will eventually stop (“respiratory arrest”). Respiratory arrest and the collapse of oxygen supply to the lungs, heart and brain (“hypoxia”) can lead to opioid-induced organ failure, injury, coma or overdose death (EMCDDA, 2016a).

1.3.2 How does naloxone reverse opioid overdose?

Pharmacodynamics describe how naloxone affects the body, capturing “events consequent on interaction of [naloxone] with its receptor or other primary site of action” (Rang et al., 2012).

Naloxone has no significant effects of its own. However, if opioids are present in the body at the time of naloxone administration, naloxone will rapidly reverse any opioid-induced effects (incl. respiratory depression and decreased consciousness) by competing and displacing opioid metabolites at the opioid receptors (see Figure 10). Reversal of respiratory depression mainly occurs at the mu-opioid receptor (Pazos & Florez, 1984). The extent of this reversal will depend on the dose of naloxone and its route of administration as well as on the dose of the opioids consumed and their receptor affinity (EMCDDA, 2016a).

In the treatment of respiratory depression, the effects of naloxone should be visible within 1–2 minutes of intravenous administration (Nguyen et al., 2012; NIH, 2007) and 3–7 minutes of intramuscular or subcutaneous (McEvoy, 2004; UNODC/WHO, 2013) administration.

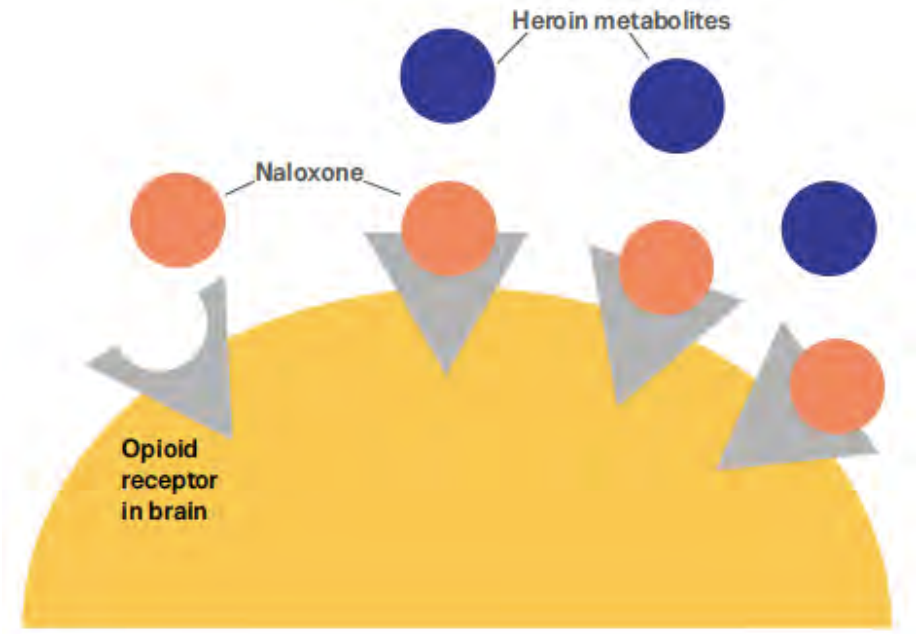

Figure 10 Naloxone competing with heroin metabolites for mu-opioid receptors[9]

In this same time interval post-dosing, naloxone administration can also precipitate moderate to severe withdrawal symptoms in opioid-dependent patients (McEvoy, 2012). Although rarely life-threatening, possible withdrawal symptoms include: abdominal cramps, body aches and weakness, diarrhea, fever, increased blood pressure irritability, nausea, nervousness, restlessness, runny nose, shivering, sweating, tachycardia, trembling, and vomiting (Martindale, 2013). The onset and severity of opioid withdrawal symptoms is more pronounced with higher naloxone doses and with intravenous administration (BMJ, 2016; Clarke, Dargan, & Jones, 2005; McEvoy, 2012). Symptoms typically subside within 1-2 hours (BMJ, 2016; McEvoy, 2012).

1.3.3 Duration of action

The duration of action of naloxone depends on its dose and route of administration. The effect of parenteral naloxone injection is typically described as lasting for up to 2-4 hours (Rang et al., 2012), with intravenous administration leading to a shorter duration of action than intramuscular administration. Kaufman et al. (1981) reported a 1.5 hours' duration of action for intravenous naloxone in volunteers who had received morphine pre-treatment. The cause of the relatively short duration of action of naloxone following

[9] Source: EMCDDA (2016a)

intravenous administration is the ease with which naloxone enters the brain and the subsequent rapid redistribution, elimination and fall in brain naloxone levels (Berkowitz, 1976).

1.3.4 Naloxone dosing

Since naloxone is a competitive antagonist, the dose required to reverse the effects of a specific opioid will depend on the opioid dose and its pharmacological properties, particularly on its receptor affinity and duration of action and (Martin, 1976). The half-lives of different opioids vary greatly, ranging from less than 10 minutes to more than 24 hours (see Table 3). In general, injection of 0.4–0.8mg of naloxone can produce a prompt reversal of opioid effects. While dosing guidelines vary at national level, the 2014 World Health Organization guidelines noted that this parenteral dose range was effective in most cases, adding that initial naloxone doses above 0.8mg increased the likelihood of significant withdrawal symptoms (WHO, 2014). The overdose victim's response should be closely monitored, and naloxone may need to be given repeatedly, since its duration of action is shorter than that of many opioids.

Table 3 Half-life of the opioids

Opioid	Approximate half-life value
Heroin (diamorphine)	6 minutes
Morphine	120 minutes
Hydromorphone	150 minutes
Oxymorphone	150 minutes
Codeine	180 minutes
Fentanyl	220 minutes
Tramadol (immediate release)	6 hours
Methadone	24 hours
Buprenorphine	37 hours

Source: Pasternak (2006)

The British National Formulary (BNF) differentiates between the administration of naloxone in medical versus non-medical settings. For medical settings, the BNF recommends the intravenous administration – or, alternatively, subcutaneous or

intramuscular administration (only if intravenous access is not feasible) – of an initial dose of 0.4mg. In case of non-response after 1 minute, dosing may be escalated as follows: “Give [0.8mg], and if still no response after another 1 minute, repeat dose of [0.8mg]; if still no response, give 2mg (4mg may be required in a seriously poisoned patient), then review diagnosis; further doses may be required if respiratory function deteriorates”. For non-medical settings, the BNF only recommends intramuscular injection, with doses of 0.4mg to be given at 2-3 minute intervals into the deltoid muscle or the anterolateral thigh until normal breathing and consciousness are restored (BNF, 2017).

1.4 The shift from intravenous to intramuscular naloxone administration

As discussed above, naloxone became the treatment of choice for reversing opioid overdose in emergency medicine. For the quickest absorption into the bloodstream and onset of action, naloxone was recommended for intravenous administration, which became standard clinical practice for nearly two decades. A 1993 publication by the World Health Organization and the Commission of the European Communities (WHO/CEC, 1993) recommended: “In patients with […] opiate poisoning, naloxone [of up to 2mg] should be given by the intravenous route until an improvement in conscious level and respiration is observed.” Hospital emergency departments routinely used naloxone intravenously for the antidote’s three indications: to reverse respiratory and central nervous system depression in opioid overdose, to reverse the therapeutic effects of opioids in medical use (e.g. after general anesthesia) and as a diagnostic tool (i.e. opioid challenge test, see above).

In the 1990s, US ambulance services started to train staff in the management of suspected opioid overdose to improve the prevention of overdose deaths in the community. Training included intramuscular naloxone administration in combination with bag–valve–mask ventilation (Sporer, Firestone, & Isaacs, 1996). Stocking ambulances with naloxone enabled staff to administer naloxone at the scene of the overdose emergency and constituted an example of ‘technology transfer’, i.e. the transfer of a development established in a specialist setting (e.g. the emergency department) to new locations (e.g. scene of overdose in the community) for more effective implementation.

However, spurred by the acquired immune deficiency syndrome (AIDS) epidemic, clinicians became increasingly wary of the risk of needle-stick injury associated with the difficulty of establishing intravenous access in people who inject drugs. The 1993

joint publication of the World Health Organization and Commission of the European (WHO/CEC, 1993) warned: “Appropriate protective precautions need to be taken by […] staff in the case of opiate addicts, bearing in mind the risk of infection from blood-borne diseases such as hepatitis B and HIV.”

As a result, there was also interest in non-injecting routes of naloxone administration as a safer alternative for use in the high-risk opioid user population. Loimer et al (1994) began to explore the feasibility of intranasal administration of naloxone (in the context of sedated detoxification and initiation onto oral naltrexone). Similarly, a Vancouver-based ambulance study by Wanger et al. (1998) compared time to recovery (interval from crew arrival to reversal of respiratory depression) between intravenous and subcutaneous administration. The study found that the slower absorption rate from subcutaneous administration was offset by the delay in establishing intravenous access in overdose victims, thus resulting in equal clinical efficacy for both routes. In addition, Horowitz (1998) noted that subcutaneous (or intramuscular) administration led to a more gradual patient recovery from overdose, compared to intravenous administration. Intramuscular naloxone administration is also associated with less rapid onset of opioid withdrawal (BMJ, 2016; McEvoy, 2012).This shift in clinical practice from intravenous towards subcutaneous and intramuscular administration of naloxone, along with the growing awareness that most overdoses are witnessed by others, set the scene for the introduction and implementation of take-home naloxone, which is the subject of Chapter 2.

Chapter 2 Twenty Years of Take-Home Naloxone

Preface

In this chapter I reconstruct historical and conceptual sequence of the development of take-home naloxone from its conception through to the present. Technology transfer of naloxone supply from standard medical settings (i.e. ambulance and emergency rooms) to layperson use constitutes the foundation of take-home naloxone distribution. Training opioid users and their peers, and also family members in overdose prevention and emergency management along with pre-provision of naloxone for emergency use (take-home naloxone) was first proposed in 1996 as a previously overlooked opportunity to prevent deaths by reducing the time between overdose onset and naloxone administration, while awaiting the arrival of an ambulance. The chapter reviews two decades of take-home naloxone research in chronological order, from its first mention in the peer-reviewed literature in 1996 up to its inclusion in the scientific summary of the United Nations General Assembly Special Session on Drugs in 2016.

Between October 2014 and December 2015, I had the opportunity to co-edit the twentieth edition of the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) Insights series, entitled “Preventing Opioid Overdose Deaths with Take-home Naloxone”, which EMCDDA had commissioned my first supervisor and me to author, in collaboration with colleagues from the Addictions Department at King’s College London. This chapter draws on content from my first-authored Chapter 4 (“Historical summary of the development and spread of take-home naloxone provision”, p. 49-68) of the Insights monograph (EMCDDA, 2016a). Contents of this chapter have also been published as first-authored manuscript in *Drug and Alcohol Dependence* (“Twenty years of take-home naloxone for the prevention of overdose deaths from heroin and other opioids – conception and maturation”; in press), in co-authorship with my first supervisor and the US historian Professor Nancy D. Campbell.

This chapter sets the scene for the systematic review of the effectiveness of take-home naloxone programs which I present in the next chapter.

2.1 Introduction

Over the past two decades, take-home naloxone has moved from its initial conceptualization as a possible harm reduction measure for preventing opioid overdose deaths to becoming an evidence-based public health strategy with organized implementation (UNODC/WHO, 2013).

In addition to naloxone, take-home naloxone programs provide overdose prevention training which may cover overdose risk factors, signs of an opioid overdose, first aid, and aftercare procedures (McAuley, Lindsay, Woods, & Louttit, 2010; Seal et al., 2005; Strang, Manning, Mayet, Best, et al., 2008).

Strong advocacy by local early adopters has enabled emergence of take-home naloxone initiatives around the world. In Italy, a harm reduction service on the outskirts of Turin reportedly provided naloxone access to clients as early as 1991 (ForumDroghe, 2016). Today, formal take-home naloxone programs exist in Australia, Canada, at least nine European countries (EMCDDA, 2016a), and the US; as well as pilots in low- and middle-income countries, including Afghanistan, China, India, Kazakhstan, Kyrgyzstan, Russia, Tajikistan, Thailand, Ukraine, and Vietnam (UNODC/WHO, 2013).

The World Health Organization issued new guidelines for community-based overdose management, suggesting that “[p]eople likely to witness an opioid overdose should have access to naloxone and be instructed in its administration” (WHO, 2014).

Despite these recent advances, dissemination of take-home naloxone remains remarkably slow. Twenty years after take-home naloxone was first proposed in 1996, only Scotland and Wales have national programs. Opioid overdose continues to account for approximately 68,000-104,000 annual deaths worldwide (UNODC, 2016b), with sharp increases reported for the UK (ISD, 2016; ONS, 2016) and US (CDC, 2016c). Many of these deaths could possibly be prevented if take-home naloxone was available. However, adequate intervention is only possible where witnesses recognize the opioid overdose. In addition to naloxone supply, it is thus essential for THN programs to teach awareness of overdose risk factors (e.g. using alone, street injection), crisis detection (e.g. snoring following opioid use may signal overdose), interim emergency care aid, and need for continued care (McAuley et al., 2010; Seal et al., 2005; Strang et al., 2008a; Strang et al., 2008b).

Take-home naloxone is now widespread in some countries, but minimal or absent elsewhere. Take-home naloxone provision is often restricted by legal and regulatory barriers. In most countries, naloxone is a prescription-only medicine and its use restricted to medical personnel or to patients to whom it is prescribed. In many countries, the

introduction of take-home naloxone provision would therefore require adjustments to current medico-legal regulations, as has occurred in the UK and elsewhere. One of the main challenges for existing take-home naloxone programs is to provide sufficient coverage of at-risk populations, so that substantial reductions in opioid overdose deaths can be achieved. Reasons for inertia and poor implementation have not been well explored.

This chapter chronicles the limitations as well as milestones and events in the emergence and evolution of take-home naloxone, from speculative harm reduction proposal to public health strategy.

2.2 Methods

2.2.1 Literature search

Medline and PsycINFO were searched for take-home naloxone-related peer-reviewed literature published between January 1990 and December 2016 using the Boolean queries: 1) “naloxone OR Narcan”; 2) “(opioid OR opiate) AND overdose AND prevention”. Database entries were not limited to English-language results. Specialist websites and databases of Public Health England, the European Monitoring Centre for Drugs and Drug Addiction, US National Institute on Drug Abuse, and United Nations agencies were also searched for take-home naloxone-related entries. Additional materials from the non-peer-reviewed literature were consulted to reconstruct the historical timeline. Information on current take-home naloxone-provision and naloxone-related legislation in Europe was gathered at the EMCDDA event “Take-home naloxone to reduce fatalities: scaling up a participatory intervention across Europe” (Lisbon, 14 October 2014). Additional information was provided by the Health Consequences and Responses Sector at EMCDDA, following consultation with EMCDDA national focal points in member states.

2.2.2 Data extraction and evidence synthesis

Take-home naloxone-related evidence was extracted and synthesized as narrative review. Relevant events were considered according to occurrence in one of four developmental phases of constructed quinquennia (with some overlap naturally occurring), which cover the 20-year period from 1996 to 2016.

2.3 Results

I present the results in four sections which discuss the following themes. Firstly, the formal articulation of the need for take-home naloxone is examined, along with preliminary testing and implementation (1996-2001). I then document early take-home naloxone schemes and challenges (2001-06). I then explore new national or state-level naloxone programs made possible through the identification and response to legal concerns (2006-11). Finally, I review the examine emergence of research studies meeting higher evidentiary standards and examine efforts to widen take-home naloxone availability (2011-16). Key events are also summarized as a chronological timeline (see Table 4).

2.3.1 1996-2001 circa: Conception and early implementation

Original articulation

Naloxone was FDA-approved in 1971 for intravenous, intramuscular, and subcutaneous administration for partial or complete reversal of opioid overdose (Garfield, 1983; Yardley, 2013) (see Table 4) and became the standard rescue medication in the emergency management of heroin overdose in hospital and ambulance settings (see Chapter 1).

However, the idea to enable opioid users and/or family and friends to take naloxone home did not arise until more than two decades after initial FDA-approval. It was first mooted at the 3rd International Harm Reduction Conference in March 1992 (Strang, 1992, 1993; Strang & Farrell, 1992) as a mere throwaway example of potential harm reduction alternatives that were being overlooked.

The first serious consideration was in the 1996 BMJ editorial (Strang, Darke, Hall, Farrell, & Ali, 1996) which identified key elements for making take-home naloxone a serious possibility, noting that take-home naloxone schemes would need to include provision to:

1) individuals at high risk of overdose, e.g. those leaving emergency care following overdose and those who lost tolerance due to detoxification, incarceration, or abstinence-based treatment;
2) patients enrolled in treatment programs (despite the protective benefits of treatment, they remain at risk); and
3) active users.

The editorial also described the poor suitability of existing naloxone products (ampoules, vials) compared to pre-filled syringes and identified medico-legal challenges raised by the prospect of third parties, such as family members, requesting or administering naloxone. Finally, the editorial urged reconsideration of naloxone's prescription-only medication status. These central points of the editorial shaped implementation and research in the subsequent years.

Early implementation

The introduction of take-home naloxone was made possible through user advocates working with physicians willing to prescribe naloxone despite medico-legal barriers. First take-home naloxone provision occurred in the late 1990s, in the US (Chicago, San Francisco), Germany (Berlin), the UK (Jersey), and Italy (Turin, Bologna, Padua).

United States

The Chicago Recovery Alliance began obtaining and distributing naloxone in 1996. Due to high user demand during a fourfold increase in drug-related deaths from 1996 to 2000, distribution by mobile van was introduced in 1998 and converted into a formal training curriculum in 2001 (Bigg, 2002; Maxwell, Bigg, Stanczykiewicz, & Carlberg-Racich, 2006).

During the late 1990s, the Chicago Recovery Alliance began discussions with harm reduction advocates in other places around starting take-home naloxone-programs and served as central clearinghouse for take-home naloxone across the US.

San Francisco Needle Exchange introduced a small-scale take-home naloxone pilot for youth in the Haight-Ashbury district in 1999 (Bigg, 2000; Giuliano, 2000; Seal et al., 2001). The pilot was later scaled up in conjunction with the DOPE (Drug Overdose Prevention and Education) project (Giuliano, 2000; Seal et al., 2001; Seal et al., 2005) and moved to be under the direction of the San Francisco Public Health Department in 2003.

Europe

Multiple sources point to undocumented or minimally documented early community-based naloxone availability in parts of Italy, notably Turin (1991) and the Emilia Romagna region (incl. Bologna, 1998) (ForumDroghe, 2016; Simini, 1998). There were reports of

take-home naloxone distribution in Padua in 1996, where a methadone clinic distributed 150 naloxone vials within 18 months. However, while overdose deaths decreased citywide, there was no formal evaluation of take-home naloxone usage (Schifano, 2001). Two pilot schemes in Berlin and the British island of Jersey (Dettmer, Saunders, & Strang, 2001) constitute the first published outcomes report on take-home naloxone provision. Between 1998 and 2000, 101 clients of a community-based drug clinic in Jersey were trained in overdose management and received take-home naloxone kits, with five reported overdose reversals (Dettmer et al., 2001). In Berlin, take-home naloxone was introduced at a mobile needle and syringe exchange scheme ("Fixpunkt") in 1999. Within 16 months, 124 take-home naloxone kits had been issued; 22 users reported administering naloxone for a total of 29 overdose reversals. The pilot was discontinued after 2002 due to lack of funding (AIDS-Hilfe, 2013; Dettmer, 2014).

Testing the notion: is the intervention necessary?

Several studies in the late 1990s and early 2000s identified situations in which naloxone should be made available:

Injecting use

In a London-based community sample of heroin users, the vast majority of reported overdoses occurred among injection users (Gossop, Griffiths, Powis, Williamson, & Strang, 1996). Injection bears a much higher risk of fatal overdose than 'chasing the dragon', snorting or oral use. It was later estimated that each year one in four injecting drug users would experience an overdose (Darke, Mattick, & Degenhardt, 2003).

Return into the community

Several international studies identified the period following release from prison as the most striking high-risk situation, with 1 in 200 prisoners with history of heroin use dying from an opioid overdose within a month of release (Bird & Hutchinson, 2003; Farrell & Marsden, 2008; Merrall et al., 2010; Seaman, Brettle, & Gore, 1998; WHO, 2010). Similar but less intense concentration of overdose deaths was observed among patients who complete in-patient detoxification (Strang et al., 2003), residential rehabilitation (Davoli, Bargagli, Perucci, Schifano, Belleudi, Hickman, Salamina, Diecidue, Vigna-Taglianti, et al., 2007), or hospital/residential treatment (Merrall et al., 2013; Ravndal & Amundsen, 2010).

Opioid substitution treatment

The first weeks on oral methadone treatment are associated with a transient increase in risk of overdose death (Caplehorn & Drummer, 1999; Cornish, Macleod, Strang, Vickerman, & Hickman, 2010; Davoli, Bargagli, Perucci, Schifano, Belleudi, Hickman, Salamina, Diecidue, Vigna-Taglianti, et al., 2007; Degenhardt et al., 2009).

Testing the notion: is the intervention acceptable for those involved?

Parallel to early take-home naloxone implementation, research assessed the feasibility and acceptability among users, carers, and providers.

Opioid users

The 1996 BMJ editorial identified opiate users as the primary target group for take-home naloxone because they are at risk of future overdose themselves and highly likely to witness and intervene in someone else's overdose. Users have expressed strong support of take-home naloxone. A London-based survey of injecting drug users (Strang et al., 1999) estimated that two-thirds of witnessed overdose deaths could have been avoided with take-home naloxone. Most respondents had already witnessed at least one overdose; 89% expressed willingness to administer naloxone in the event of an overdose; 70% agreed with the proposal that naloxone should be provided; and nearly 90% of those who had witnessed an overdose stated that they would have used the medication had it been available.

Subsequent surveys reported willingness among users to be trained in overdose management and naloxone administration (Bennett & Higgins, 1999; Best et al., 2002; Kerr, Dietze, Kelly, & Jolley, 2008; Lagu, Anderson, & Stein, 2006; Seal et al., 2003; Strang, Best, Man, Noble, & Gossop, 2000; Worthington, Markham Piper, Galea, & Rosenthal, 2006).

In the first published evaluation of take-home naloxone training, Seal and colleagues (2005) assessed knowledge of overdose management by asking participants to name risk factors, signs of overdose, and overdose prevention and management strategies. A significant increase in overdose-related knowledge was maintained at 6-month follow-up (Seal et al., 2005).

However, opioid users also expressed concerns about take-home naloxone, such as fear of experiencing withdrawal symptoms, enabling further drug use, risk of blood-borne virus infection, and potentially having to manage agitation and hostility in those revived (Kerr, Dietze, Kelly, et al., 2008; Seal et al., 2003; Worthington et al., 2006). Service users also expressed concerns about the risk of confiscation of the antidote and its potential role in escalating already delicate relationships with law enforcement (Richert, 2015; Seal et al., 2003; Worthington et al., 2006).

Carers

Most opiate overdoses occur at private homes and/or in presence of peers, family members, and partners (Best et al., 2002; McGregor, Darke, Ali, & Christie, 1998). Constituting a potential intervention resource, close contacts of users are thus the second target group for take-home naloxone and training. In an England-based postal survey of family members (Strang, Manning, Mayet, Titherington, et al., 2008), the majority reported strong interest in take-home naloxone. A recent waiting-list randomized trial (Williams, Marsden, & Strang, 2014) demonstrated good improvements in the knowledge and competence of carers in overdose management, which were maintained at 3-month follow-up.

Health care providers

Early US-based studies explored health care providers' attitudes to take-home naloxone. A postal survey (Coffin et al., 2003) of New York-based clinicians with prescribing authority showed that over a third were willing to prescribe naloxone. Negative attitudes were revealed in surveys of Baltimore-based emergency service providers (Tobin, Gaasch, Clarke, MacKenzie, & Latkin, 2005) and physicians throughout the US who were likely involved in treatment of opioid users (Beletsky et al., 2007): most believed take-home naloxone would not reduce drug-related deaths and reported they would never consider prescribing naloxone. Common concerns included potential promotion of drug use (Ashworth, 2006; Tobin et al., 2005), risk of unsafe needle disposal (Tobin et al., 2005), and users' competency in administration (Ashworth, 2006; Byrne, 2006; Tobin et al., 2005). Providers voiced strong concerns over uncertain medico-legal status and potential liability issues (Burris, Norland, & Edlin, 2001).

In the coming years, community-based naloxone would be adopted by firefighters and the police. The unanticipated uptake by these workforces may have positively influenced public opinion, including attitudes among health care providers.

2.3.2 2001-2006 circa: Modest progress amidst legal and safety concerns

Following the pioneering Chicago Recovery Alliance program, early adopters in the US included New Mexico, which began take-home naloxone distribution in early 2001 (Baca, 2001; Baca & Grant, 2005).

In 2004, the Baltimore Staying Alive Drug Overdose Prevention Program was launched, sponsored by the Baltimore City Health Department and Open Society Institute, and the Lower East Side Harm Reduction Coalition in New York conducted a pilot in 2004, which was expanded to all city-funded Syringe Exchange Programs in 2005 (Heller & Stancliff, 2007).

There were also reports of take-home naloxone distribution in Barcelona as early as 2001, which led to around 60 successful overdose reversals (Trujols, 2001). In mainland UK, take-home naloxone was first introduced in South London in 2002 (McDonald et al., 2016).

Support was rarely encountered in the treatment field, where the take-home naloxone debate was dominated by legal and safety concerns, such as: (i) might naloxone availability encourage heroin use?; (ii) could it discourage users from calling an ambulance; and (iii) would naloxone's short half-life result in rebound overdose after the initial dose wore off?

Early surveys of drug users found that take-home naloxone was unlikely to lead to increased heroin consumption (Strang, 1999), a finding recently confirmed in a large US retrospective cohort study (n=4,926) (Doe-Simkins et al., 2014). Similarly, in a Danish study, death from (presumed) 'rebound' overdose toxicity occurred only in 3 out of 3,245 cases of naloxone administration (Rudolph et al., 2011). Low rates of ambulance calls after take-home naloxone administration have been observed (Bennett & Holloway, 2012); but use of emergency medical services can be encouraged in take-home naloxone training (Bennett & Holloway, 2012; Strang, Manning, Mayet, Best, et al., 2008).

Legal analyses of Take-Home Emergency Naloxone provision

An early US legal analysis (Burris et al., 2001) found that providers' risk of malpractice liability associated with prescribing take-home naloxone was no greater than for general health care provision. Nonetheless, many prescribers have remained wary of prescribing take-home naloxone (NPHL, 2014).

Prescribing take-home naloxone to an at-risk patient for administration by a trained partner/family member is analogous to the pre-provision of anti-epileptic medication or injectable adrenaline/epinephrine (EpiPen). However, in situations where naloxone is being prescribed without specific knowledge of who will administer or be administered naloxone, the legal situation becomes murky. Professionals have expressed anxieties about patients' 'deputation' as health care providers when injecting naloxone (Burris et al., 2001); medical providers and service users alike raised concerns about civil or criminal liability (Lenton & Hargreaves, 2000).

2.3.3 2006-2011 circa: Identification of legal pathways for THN

Responses to legal barriers

Because take-home naloxone has come about so recently, most medico-legal barriers to it were unintended consequences of prior legislation passed for other purposes (NPHL, 2016). About ten years after the original take-home naloxone proposal, some jurisdictions began to pass laws to facilitate take-home naloxone implementation. Policies are typically of two kinds: those that enable naloxone access either via broad standing orders, or amendment of Good Samaritan legislation that widens immunity to encompass not only physicians but also first responders, bystanders, or witnesses who extend care in emergency situations.

United Kingdom

In the UK, parenteral (injectable) medicines can be administered only by patients themselves, or by 'an appropriate practitioner or a person acting in accordance with the directions of an appropriate practitioner' (s.58(2)(b) Medicines Act 1968), (Government, 1968). However, following endorsement of take-home naloxone provision by the Advisory Council on the Misuse of Drugs (ACMD, 2000), naloxone was incorporated into the Schedule 7 of the UK Medicines Act in 2005, which allowed any member of the general public to administer naloxone with the aim of saving a life. Thereby, naloxone was placed alongside other rescue medications, such as glucagon, adrenaline and snake antivenin (Strang, Kelleher, Best, Mayet, & Manning, 2006). Naloxone could then lawfully be given by a witness to an overdose victim to whom it was not prescribed, opening doors to naloxone administration by layperson first-responders. At least 16 sites then implemented take-home naloxone pilots in England (NTA, 2011).

However, naloxone remained a prescription-only medication. The UK Department of Health 'Orange Guidelines' (DOH, 2007) stated: *"naloxone […] must be prescribed to named patients or supplied to an individual by means of a patient group direction."*

In 2012, ACMD urged the Department of Health to review naloxone's prescription-only status (ACMD, 2012). Triggered by this request, the Medicines and Healthcare Products Regulatory Agency (MHRA) released a consultation in 2013, asking for feedback on a proposal to increase community-based naloxone access (MHRA, 2013). Thus, new UK legislation was passed in late 2015 which explicitly enabled wider availability to drug users, family members, other carers, and staff working in relevant treatment and social care agencies. New Public Health England (PHE) guidelines exempted naloxone from the usual prescription requirement when it is supplied by a drug service commissioned by a local authority or NHS (PHE, 2015).

United States

In the US, naloxone is a prescription-only-medication at federal level, although there is considerable variation due to state-level legislation and lower-court rulings. New Mexico became the first state to remove legal barriers to take-home naloxone prescribing and distribution in 2001 (Alcorn, 2014) and to grant legal immunity to bystanders in 2007 via a "Good Samaritan" law. New York and Connecticut followed with laws that granted immunity from civil liability to healthcare providers with prescribing authority (Sporer & Kral, 2007).

Established in 2006, the Massachusetts take-home naloxone pilot program used a standing order to enable public health care workers to provide take-home naloxone without a prescription (Doe-Simkins, Walley, Epstein, & Moyer, 2009). The standing order model allows a lead physician within a given jurisdiction to issue a written order that naloxone can be distributed by designated pharmacists or other qualified professionals (OSF, 2013).

At the end of the 2000s, there were fewer than three dozen take-home naloxone programs in the US, but the number had increased more than fivefold by 2014 (OSF, 2013) – operated by community-based organizations, public health departments, and Veterans Health Administration facilities (Humphreys, 2015).

Amid growing public support, organizations including the US Conference of Mayors, the American Medical Association, the American Public Health Association, and the National Association of Boards of Pharmacy urged states to remove legal barriers to take-home naloxone (Alcorn, 2014; NPHL, 2016). As of June 2016, forty-eight states had amended

laws to relieve provider liability when prescribing or dispensing naloxone, and thirty-seven states had passed Good Samaritan laws (both including the District of Columbia) (Burris et al., 2001; DOJ, 2014; NPHL, 2014, 2016). Sustainability has been achieved in several states (CDC, 2012b).

As of mid-2014, 136 take-home naloxone programs were providing naloxone kits to laypersons at 644 sites across the country, with naloxone kits supplied to a total of 152,283 clients and 26,463 reported overdose reversals since 1996 (CDC, 2015).

First national and state-wide programs

In the late 2000s, first take-home naloxone programs expanded coverage from a local to a state-wide or national level.

Catalonia

Following underground distribution of naloxone in the early 2000s, the public health agencies of Barcelona and the autonomous region of Catalonia formally launched a take-home naloxone program in 2008 (EMCDDA, 2016a). Barcelona is considered to have the highest mortality rate in Spain (EMCDDA, 2016a).

The Catalonian take-home naloxone program was integrated into the Catalan Drug Abuse Care Centers Network (XADC), which covers drug-treatment centers, therapeutic communities, detox units, and drug-consumption rooms. At participating sites, staff and clients could receive training in overdose prevention and naloxone kits. Clients received a financial incentive to attend training. As of December 2013, 1,007 professionals and 4,738 injecting drug users had been trained, with 5,830 naloxone kits distributed since 2008. Among those who received naloxone and witnessed an overdose, 40% reported using the naloxone kit. In a cross-sectional study of 306 opioid users in Catalonia, 44% reported having participated in an overdose prevention program (Arribas-Ibar, Sánchez-Niubò, Majó, Domingo-Salvany, & Brugal, 2014), suggesting substantial coverage of the target population. However, the impact of take-home naloxone provision on overdose mortality rates could not be determined, since overdose deaths in Catalonia had been decreasing since well before the start of the take-home naloxone project.

Scotland

Three local take-home naloxone pilots were launched in Glasgow, Lanark and Inverness during or after 2007 (McAuley, Best, Taylor, Hunter, & Robertson, 2012). In 2011, the Scottish Procurator Fiscal issued a “Letter of Comfort”, granting immunity to pharmacists who supplied naloxone without prescription to staff working at services with a high rate of overdoses (e.g. hostels) (Angiolini, 2011). By allowing naloxone storage in non-medical facilities for emergency use, these so-called ‘Lord Advocate’s guidelines’ facilitated introduction of the Scottish National Naloxone Programme in 2011 (ACMD, 2012).

The program involves take-home naloxone distribution in the community and to prisoners on release. Services can issue take-home naloxone to staff, persons at risk of overdose, family members, and peers (with documented consent of the person at risk). The Scottish government has funded the program centrally, reimbursing all service providers for the number of naloxone kits issued. Scotland has its own registry for drug-related deaths, which enables the Scottish National Naloxone Programme to track the number of opioid overdose deaths in relation to the number of take-home naloxone kits in circulation.

The Scottish National Naloxone Programme issued a total of 8,146 naloxone kits during a 12-month period in 2015/16; 7,214 (89%) in the community and 932 (11%) to prisoners on release (ISD, 2016).

Among Scottish prisoners supplied with take-home naloxone, mortality within 4 weeks after release had decreased to 4.7% by 2015, compared with the pooled 2006–10 baseline of 9.8% (ISD, 2016). The reduction of heroin-related deaths within 4 weeks of prison release coincides with a steady increase in the number of take-home naloxone kits provided since start of the Scottish National Naloxone Programme. The significance of this reduction has been examined (Bird, McAuley, Perry, & Hunter, 2016), with study rationale as described by (Bird, Parmar, & Strang, 2015).

Despite more than doubling of the volume of take-home naloxone kits in Scotland (i.e. from 52 kits per 1,000 problem drug users in 2011/12 to 132 per 1,000 in 2015/16), the percentage of all opioid-related deaths occurring among people who had been discharged from hospital in the previous four weeks has remained largely unchanged at around 10% (ISD, 2016).

Wales

Following the 2007 introduction of a take-home naloxone pilot, Wales launched a national naloxone program in 2011 (Bennett & Holloway, 2012). Between mid-2009 and

early 2014, 4,579 take-home naloxone kits were issued and reportedly used in 375 overdose events (McDonald et al., 2016). In an effort to increase the volume of take-home naloxone kits in circulation, 1,802 kits were issued in Wales in 2013/14 alone; with 150 overdose reversals recorded in the same period. The Welsh take-home naloxone program tracks overdose prevention training and the provision of take-home naloxone kits in a national Harm Reduction Database, which subsumes local data from 37 registries across Wales.

Massachusetts

The Massachusetts Department of Public Health has conducted the most comprehensive U.S. program evaluation to date. Boston-based harm reduction activists began take-home naloxone distribution in the early 2000s without formal approvals and documented the number of naloxone vials distributed and overdose events reversed in a 2005 letter to the mayor of Boston who facilitated a joint meeting between the activists and the Department of Public Health. As a result, Boston Public Health Commission authorized development of a take-home naloxone program via its mobile needle-exchange scheme in 2006. The Massachusetts take-home naloxone program was the first to involve distribution of intranasal naloxone and to allow non-medical public health workers to issue naloxone. By 2009, the Massachusetts Department of Public Health had expanded the program to seven more communities, operating out of needle-exchange sites, methadone clinics, homeless shelters, inpatient detoxification programs, community meetings, outpatient and residential addiction-treatment programs, and emergency departments. By 2014, the Massachusetts take-home naloxone program had trained 4,926 drug users, of whom 373 reported administering naloxone (Doe-Simkins et al., 2014).

2.3.4 2011-2016 circa: Emergence of stronger data and expansion

Encouraged by the WHO Guidelines and the emergence of more robust evidence, many countries began to introduce take-home naloxone projects in the early and mid -2010s.

<u>Dissemination and expansion</u>

Australia

Despite immediate endorsement of the original take-home naloxone proposal by Australian researchers (Darke & Hall, 1997; Fry, Dietze, & Crofts, 2000; Lenton & Hargreaves, 2000), funding for an early naloxone trial in Victoria was affected by the

2000 Australian heroin drought (Dietze, 2016). Intranasal naloxone was explored in ambulance-based trials (Kelly et al., 2005; Kerr, Kelly, Dietze, Jolley, & Barger, 2009), but take-home naloxone was halted by medico-legal concerns.

Following the emergence of findings from take-home naloxone schemes overseas, Australian researchers reiterated the case for take-home naloxone (Dietze & Lenton, 2010; Lenton, Dietze, Degenhardt, Darke, & Butler, 2009), which ultimately led to the launch of I-ENNAACT, the first Australian take-home naloxone program in Canberra, in late 2011.

A preliminary evaluation in late 2014 showed that over 200 injecting drug users had been trained in overdose prevention (including 18 inmates) and reported 57 successful overdose reversals (Dietze, 2016). Naloxone access in Australia was facilitated by the 2012 addition of the antidote to the government Pharmaceutical Benefit Scheme which subsidizes prescription drugs. Australian residents can now obtain naloxone at a concession rate of AUD 5.90, rather than the previous AUD 60 (Fowlie, 2013). The Australian Medical Association endorsed take-home naloxone in 2013 (Anex, 2013), and naloxone was re-classified / scheduled as over-the-counter medication in 2016 (Lenton, Dietze, & Jauncey, 2016). Take-home naloxone scale-up in New South Wales is currently underway (Dietze, 2016).

Europe

In the early 2010s, several northern European countries launched take-home naloxone projects: Denmark and Estonia in 2013, with Norway following in 2014 and Ireland in 2015 (EMCDDA, 2016a).

Denmark: During the 1990s and 2000s, an average 250–275 drug overdose deaths were registered in Denmark annually, mostly from methadone and heroin.

Because of the high number of opioid-related overdoses, the Danish Ministry of Health decided in 2012 to introduce a take-home naloxone program which launched in March 2013 (EMCDDA, 2016a) and was implemented out in four municipalities (Copenhagen, Aarhus, Odense and Glostrup) with high prevalence of opioid use.

The Danish take-home naloxone kits are unique in that they contain a 2mg/2ml pre-filled naloxone syringe in combination with both the mucosal atomizer device for nasal administration (i.e., similar to the Massachusetts program) as well as a needle for intramuscular injection in case of non-response to the nasal spray (EMCDDA, 2016a).

Trainees are instructed to regard the 2-mg/2ml formulation as five doses of 0.4mg each: the first three doses are for intranasal administration and, in case of non-response, the fourth and fifth doses should be used for intramuscular administration. As of October 2014, 121 take-home naloxone kits had been distributed, with seven reported overdose reversals. While there has been a downward trend in drug-related deaths in Denmark, the uncontrolled evaluation design of the Danish take-home naloxone program does not allow for assessment of its impact on mortality outcomes.

Estonia: Estonia has the highest drug-related mortality rate in the European Union, with 111 deaths per million adult inhabitants in 2013. Unlike other European countries, most drug overdose fatalities are associated with the use of fentanyl (EMCDDA, 2012). In September 2013, the National Institute for Health Development launched a government-funded take-home naloxone program in Harju and East-Viru, i.e. the two counties with the highest prevalence of injection drug use. Based on the model of the Scottish National Naloxone Programme, patient lists are generated (instead of individual prescriptions) and the distribution of naloxone kits is logged to comply with national legislation. As of October 2014, 552 naloxone kits had been distributed, which led to 72 repeat prescriptions and 71 overdose reversals (EMCDDA, 2016a).

Norway: In response to some of the highest per capita overdose mortality rates in Europe with 70 overdose deaths per million adult inhabitants (EMCDDA, 2012), the Norwegian Minister for Health launched the national overdose-prevention campaign in April 2014. The campaign covers a 5-year overdose-prevention strategy, including take-home naloxone distribution. The Norwegian take-home naloxone pilot, which launched in June 2014, is run out of low-threshold health and care facilities in Bergen and Oslo, as well as housing facilities, drop-in day centers and mobile services. Similar to the Massachusetts take-home naloxone program, participants receive a 2-mg/2ml pre-filled syringe equipped with a mucosal atomization device. Unlike the Danish pilot, the Norwegian naloxone kit does not contain a needle for naloxone injection, and only intranasal administration is possible. Since no needles are provided, no individual prescription is needed. Special approval from the Norwegian drugs regulatory authority was required to distribute the off-label naloxone nasal spray formulation. Between program start in mid-2014 and late 2015, the Norwegian take-home naloxone program distributed 2,056 nasal kits, with 277 overdose reversals reported (Madah-Amiri, Clausen, & Lobmaier, 2017).

Ireland: In Ireland, the number of drug-related deaths increased from 105 in 2003 to 181 in 2012. Most overdose fatalities registered in 2012 were opioid-related, and toxicology results revealed that methadone was present in more cases than heroin (EMCDDA, 2012). More than a decade after the Irish National Advisory Committee on Drugs (NACD) explored of the feasibility of take-home naloxone implementation in Ireland which was not pursued at the time (NACD, 2003), the Irish Health Service Executive announced In October 2014 that it would fund a take-home naloxone demonstration project with an initial target sample size of 600 opioid users (Sheehan, 2014). The launch of the project took place in May 2015 (Health, 2015). As of 2016, a total of 95 naloxone prescriptions had been issued, of which two-thirds in Dublin in one third Limerick, with a total of five overdose reversals reported (A. Clarke & Eustace, 2016).

Exploration of new settings and workforces

Community-based harm reduction teams have been the 'default' resource for take-home naloxone provision, with users and their primary carers the main target populations. The CDC survey (2015) of current take-home naloxone programs in the US reported that most program participants are people who use drugs (82%), with friends and family members being the second most common group (12%). Over the past five years, researchers have sought to study whether expansion of the take-home naloxone intervention to new settings and workforces could enhance its impact.

Police and firefighters

In the US, several jurisdictions have passed legal provisions to authorize nonmedical first responders to administer naloxone (Banta-Green, Beletsky, Schoeppe, Coffin, & Kuszler, 2013). In 2010, Massachusetts was the first state to pioneer equipping firefighters and police with naloxone (Davis, Ruiz, Glynn, Picariello, & Walley, 2014), and the Obama administration's National Drug Control Strategy (ONDCP, 2010) urged expansion of law enforcement professionals and firefighters "who are trained in how to recognize an overdose and who further know how to administer […] naloxone." Law enforcement officers can be successfully trained to respond to overdose (Saucier, Zaller, Macmadu, & Green, 2016; Wagner, Bovet, Haynes, Joshua, & Davidson, 2016) and report positive attitudes (Goodman & Hartocollis, 2014; Ray, O'Donnell, & Kahre, 2015). Over 220 law enforcement agencies across 24 U.S. states carry naloxone (Davis, Carr, Southwell, & Beletsky, 2015). Equipping Ohio police with naloxone nasal spray was associated with a decline in opioid overdose deaths (Rando, Broering, Olson, Marco, &

Evans, 2015). A New York-based program reported over 100 overdose rescues within a year (NYAG, 2015). However, studies reveal geographical disparities, with naloxone equipment of emergency responders more common in urban than rural settings (Rando et al., 2015). In Europe, police officers have been included as target population in the Norwegian take-home naloxone program (EMCDDA, 2016a).

Primary care

U.S. primary care providers have described insufficient time during patient appointments and inability to follow up with patients as main organizational barriers to take-home naloxone (Binswanger et al., 2015). However, a San Francisco study of primary care patients receiving long-term opioid pain therapy found that naloxone co-prescribing was feasible and associated with significantly reduced opioid-related emergency department visits at 1-year follow-up (Coffin et al., 2016).

Emergency care

The Massachusetts take-home naloxone program provides naloxone at emergency departments, and feasibility has recently also been explored elsewhere. A British Columbia survey of emergency department patients at risk of opioid overdose (Kestler et al., 2017) found that two-thirds accepted take-home naloxone kits when offered to them at the emergency department, highlighting the potential of this setting for overdose prevention.

Prison release

Take-home naloxone provision on prison release was the focus of the N-ALIVE randomized trial in England and Wales, which assessed its impact on overdose mortality in the month post-release (Bird & Hutchinson, 2003; Farrell & Marsden, 2008; Strang, Bird, & Parmar, 2013). N-ALIVE pilot with its target recruitment of 2,800 subjects yielded a marked decrease in opioid-related deaths, a subsequent large-scale trial involving 28,000 prisoners on release was scheduled. However, the pilot was ended prematurely in December 2014 (total enrolment: 1,685 subjects) (Parmar, Strang, Choo, Meade, & Bird, 2017) after it became clear that many of the overdoses being reversed by naloxone were not among the study subjects being followed up, and after separate monitoring of the Scottish National Naloxone Programme showed a significant reduction in the

proportion of opioid-related deaths in the month following prison release (see above) (Bird et al., 2016).

Prison-based take-home naloxone has also been introduced and studied in New York City, California, and Rhode Island (Green et al., 2015; Jordan, 2015; Rosner, 2015).

A growing evidence base

By the 2010s intervention studies typically reported the number of overdoses reversed with naloxone as a central outcome; high naloxone usage rates confirmed the 'trainability' of heroin users to adequately respond to overdose (Green, Heimer, & Grau, 2008; Lopez-Gaston, Best, Manning, & Day, 2009; Markham-Piper et al., 2008; McAuley et al., 2010; Strang, Manning, Mayet, Best, et al., 2008; Tobin, Sherman, Beilenson, Welsh, & Latkin, 2009; Wagner et al., 2010). However, methodological limitations such as small sample sizes, uncontrolled designs, lack of randomization and systematic follow-up made it difficult to quantify the impact of take-home naloxone provision on overdose mortality.

In 2012, the United Nations Commission on Narcotic Drugs passed Resolution 55/7 (UNODC, 2012), which identified need for more effective prevention of drug overdose and "[e]ncourage[d] all Member States to include effective elements for the prevention and treatment of drug overdose, in particular opioid overdose, in national drug policies, including the use of opioid receptor antagonists such as naloxone." The same year, N-ALIVE, i.e. the first large-scale randomized trial of take-home naloxone provision, started recruitment (Strang et al., 2013).

In 2013, two cost-effectiveness analyses presented modelling data from the US and Russia, concluding that take-home naloxone was cost-effective even when the cost of naloxone increased and the rate of observed overdoses decreased (Coffin & Sullivan, 2013a, 2013b). Another 2013 study addressed the impact of take-home naloxone provision on local overdose rates using an interrupted-time series analysis, finding that Massachusetts-based communities with take-home naloxone provision had significantly lower overdose mortality rates than communities without (Walley, Xuan, et al., 2013).

These results were among the key evidence included in a WHO review of community-based naloxone, which led to the November 2014 launch of the WHO Guidelines on the Community Management of Opioid Overdose (WHO, 2014).

The key recommendation was that "[p]eople likely to witness an opioid overdose should have access to naloxone and be instructed in its administration" (WHO, 2014).

Subsequently, a BMJ editorial was published, arguing that there is "[n]ow enough experience to justify [take-home naloxone implementation]" (Strang, Bird, Dietze, Gerra, & McLellan, 2014). Following release of the WHO Guidelines, three systematic reviews (Clark, Wilder, & Winstanley, 2014; EMCDDA, 2015; McDonald & Strang, 2016) reached similar conclusions. Clark et al. (2014) found that participation in take-home naloxone programs led to improved overdose-related knowledge and appropriate use and administration of naloxone. The EMCDDA (2015) concluded: 'there is evidence that educational and training interventions with provision of take-home naloxone decrease overdose-related mortality' (p. 11). The most recent systematic review (McDonald & Strang, 2016) assessed the safety of take-home naloxone programs as well as their impact on opioid overdose-related mortality using the Bradford Hill criteria (Hill, 1965) (see Chapter 3).

Finally, in April 2016, the United Nations General Assembly Special Session on Drugs (UNGASS 2016) included "naloxone distribution to prevent overdose deaths associated with opioid use" as example of evidence-based strategies in its scientific summary (UNODC, 2016a).

2.4 Discussion

2.4.1 Statement of principal findings

This chapter traces the development of take-home naloxone over twenty years, from its conception up to its current role.

2.4.2 Strengths and weaknesses of the chapter

To allow for the wide scope of this literature review, a broad search strategy was applied. While the search strategy was not limited to English-language entries, it is possible that relevant international sources (published in other languages) may have been overlooked. Take-home naloxone initiatives in non-English speaking countries may thus be underrepresented in this literature review. Apart from a program description of take-home naloxone provision in Kyrgyzstan and Tajikistan (Kan et al., 2014), take-home naloxone initiatives in low and middle-income countries largely missing from the peer-reviewed literature. A second limitation concerns the possibility that that the chronological timeline (see also Table 4) may include minor inaccuracies due to conflicting information in some source documents.

2.4.3 Questions for future research

After two decades of take-home naloxone research, many questions still remain unanswered about the intervention, including questions about suitable non-injectable routes of naloxone administration and optimal dose range (FDA, 2016b). These questions are discussed in more detail in Chapters 4 to 9.

2.5 Conclusion

Twenty years ago, the very idea of take-home naloxone was a radical speculative proposal to extend harm reduction beyond needle and syringe exchange. Take-home naloxone has subsequently overcome legal barriers in many jurisdictions and is increasingly accepted as an effective public health strategy to reduce overdose fatalities. In the next chapter, I will present my systematic review of the effectiveness of take-home naloxone programs, which has contributed to the evidence-base for the intervention.

Table 4 Key events in the emergence and evolution of THN

Year	Month	Country	Event
1961	March	USA	Drs. Jack Fishman and Mozes J. Lewenstein apply for first US patent for synthesis of naloxone (issued in May 1966)
		USA	Dr. Harold Blumberg and colleagues publish abstract in *Federation Proceedings* in which he introduces naloxone as "potent, rapid-acting, and relatively pure narcotic antagonist."
1962	March	UK	Sankyo applies for British patent for naloxone (issued in October 1963)
		Japan	Minakami et al. of Sankyo Company Ltd. Publish first full-length journal article on naloxone in *Life Sciences*
1971		USA	FDA licenses naloxone as prescription-only medication; naloxone enters clinical practice in Europe in subsequent years
1983		Int'l	Naloxone is included in the 1983 WHO List of Essential Medicines (and subsequent editions)
1991		Italy	Report of community-based naloxone access in Turin suburb
1992	March	Australia	Notion of THN provision to at-risk populations is mooted at 3rd International Harm Reduction Conference in Melbourne
1996	June	UK	*BMJ* editorial by Strang et al. states 'home-based supplies of naloxone would save lives'
	ca. June	USA	Chicago Recovery Alliance (CRA) distributes first THN kits
		Italy	Ministry of Health classifies naloxone as over-the-counter medication
		Italy	Reports of THN distribution in Padua
1998	September	Italy	Simini announces plans to distribute THN in Bologna and surrounding Emilia Romagna region in *The Lancet*
	October	UK	Island of Jersey starts THN distribution
1999	January	Germany	Fixpunkt Berlin starts THN distribution
	March	USA	San Francisco Needle Exchange starts THN distribution
2001	April	Germany/ UK	First published report of THN distribution by Dettmer et al. in *BMJ*
		Spain	Reports of underground THN distribution in Barcelona
		USA	New Mexico launches THN program
		UK	Introduction of first mainland THN scheme (south London)
2002	March	USA	Dan Bigg of CRA reports first lives saved using THN in *BMJ*
2003		USA	San Francisco Public Health Dept. starts THN program
2004	June	USA	Lower East Side Harm Reduction Coalition in New York starts THN distribution
		USA	Baltimore launches Staying Alive Drug Overdose Prevention Program

Year	Month	Country	Event
2005	November	UK	Legal status of naloxone changed to permit emergency administration of naloxone by any member of the general public (Schedule 7 of the Medicines Act)
2006	August	USA	Boston Public Health Commission authorizes start of THN program, including provision of intranasal naloxone kits
2006		UK	National Treatment Agency for Substance Misuse (NTA) funds THN training pilot in 16 sites in England
2007		UK	Scotland and Wales establish THN pilots
2008		UK	Medical Research Council funds N-ALIVE trial
		Spain	Formal THN program launched in Barcelona
2010		USA	ONDCP National Drug Control Strategy endorses community use of naloxone
	November	UK	Scotland launches national THN program
2011		UK	Scottish Lord Advocate issues new guidelines
		UK	Wales launches national THN program
		Australia	First Australian THN program starts in Canberra
2012	March	Int'l	UNODC Resolution 55/7 states 'opioid overdose treatment, including the provision of opioid receptor antagonists such as naloxone, is part of a comprehensive approach to services for drug users'
	April	USA	FDA, CDC, NIDA, and HHS convene naloxone meeting
	May	UK	Advisory Council on the Misuse of Drugs urges Department of Health to review naloxone prescription-only status
	December	Australia	Naloxone is added to the Pharmaceutical Benefit Scheme
2013	March	Denmark	THN program starts (dual kits: intranasal and injectable)
		Estonia	Harju and East-Viru counties start THN distribution
2014	July	Norway	THN program starts (intranasal)
	November	Int'l	WHO releases guidelines on the community management of opioid overdose
2015	May	Ireland	Health Services Executive approves THN by prescription, THN project starts
	October	UK	Public Health England release guidelines allowing drug services to issue THN without prescription
	November	USA	FDA approves a first naloxone nasal spray product
2016	February	Australia	Injectable naloxone becomes available over-the-counter
	April	Int'l	UNGASS 2016 includes naloxone in its scientific summary
	October	Canada	Health Canada approves naloxone nasal spray product without prescription requirement
	October	USA	FDA convenes meeting to discuss naloxone dosing standards

Chapter 3 Bradford Hill Analysis of Take-Home Naloxone

Preface

In this chapter, I review the evidence for take-home naloxone programs by means of a Bradford-Hill analysis. Due to the current lively debate around take-home naloxone and associated public health implications, I considered it important for the data from take-home naloxone programs to be reported in their entirety.

The idea for this chapter emerged in 2013 when the Australian researcher Dr. Alex Wodak published a blog post (Wodak, 2013), wherein he voiced skepticism regarding the effectiveness and safety of take-home naloxone. Despite his roots in the harm reduction movement, Dr. Wodak argued that – in the absence of results from randomized controlled trials – the "existing evidence for the effectiveness and safety [of take-home naloxone] was weak" and suggested that implementation of THN should be delayed until stronger evidence became available. Dr. Wodak called on the research community to provide the lacking evidence by conducting a Bradford Hill analysis, having previously himself applied this method to the study of needle-and-syringe programs.

I used the contents of this Bradford Hill analysis as the basis of a first-authored paper entitled "Are take-home naloxone programmes effective? Systematic review utilizing application of the Bradford Hill criteria" that was published in Addiction in March 2016. In addition, prior to publication of the paper, I was invited to present the results of my study as part of a naloxone symposium at the annual meeting of the Society for the Study of Addiction (SSA) in November 2015. After accessing the PowerPoint slides and audio recording of my presentation on the SSA website, Dr. Wodak issued a public statement to the effect that, with my SSA presentation of the Bradford-Hill analysis, he considered that the scientific case had now adequately been made. Dr. Wodak's email to me (December 17, 2015) stated: "[I am] even more delighted (but not surprised) to read that your assessment is that the available evidence meets all but two of the criteria". As recently as January 2016, Dr. Wodak has been quoted as "welcom[ing] the increased availability of the antidote" in Australia (Davey, 2016).

According to the Addiction editorial office, my Bradford Hill analysis ranks among the top 0.1% of most downloaded papers in the journal in the year 2016. The US FDA also presented my analysis as key evidence for the effectiveness of take-home naloxone at their public meeting in October 2016 (FDA, 2016a).

3.1 Introduction

As discussed in Chapter 2, take-home naloxone (THN) programs have over the past 20 years been implemented in Europe, Northern America, Asia, and Australia (UNODC/WHO, 2013). However, the vast majority of evaluations have been pilot schemes with uncontrolled study design.

The evaluation of THN programs is challenging: randomized controlled trials (RCTs) are often considered the gold standard of scientific study of clinical impact, but conducting such trials in this context would often be unethical and fraught with methodological difficulties given the infrequency and unpredictability of overdose.

Critics of THN programs argue that the existing observational data are not strong enough to infer causation from naloxone provision to the reduction of overdose deaths (Byrne, 2006; Wodak, 2013). A counter-argument may be that similar reservations initially blocked other harm reduction strategies, including needle exchange programs and opioid substitution therapy (Des Jarlais, Paone, Friedman, Peyser, & Newman, 1995) that are now evidence-based practice (Bazazi, Zaller, Fu, & Rich, 2010) (and would still be absent if the precautionary principle had been strictly applied).

A better understanding of the potential benefits and risks of THN provision is essential. If concerns are valid, they need to be identified and considered in context. But mere assertions of hypothetical disadvantages must not prohibit access to a life-saving medication. A previous systematic review (Clark et al., 2014) found that participation in THN programs led to improved overdose-related knowledge as well as appropriate use and administration of naloxone, but the impact on overdose mortality was not assessed.

The goal of this Bradford Hill analysis is to assess the effectiveness of THN programs by rigorously following a well-recognized process (i.e. the Bradford Hill criteria) to evaluate the data within eligible studies. The analysis was conducted with two specific aims:

- Aim 1: to describe the impact of THN provision on overdose-related mortality in opioid users;
- Aim 2: to assess the safety of THN provision by quantifying adverse events associated with naloxone administration.

3.2 Methods

A systematic literature search was performed following PRISMA guidance (see Figure 11for PRISMA flow diagram).

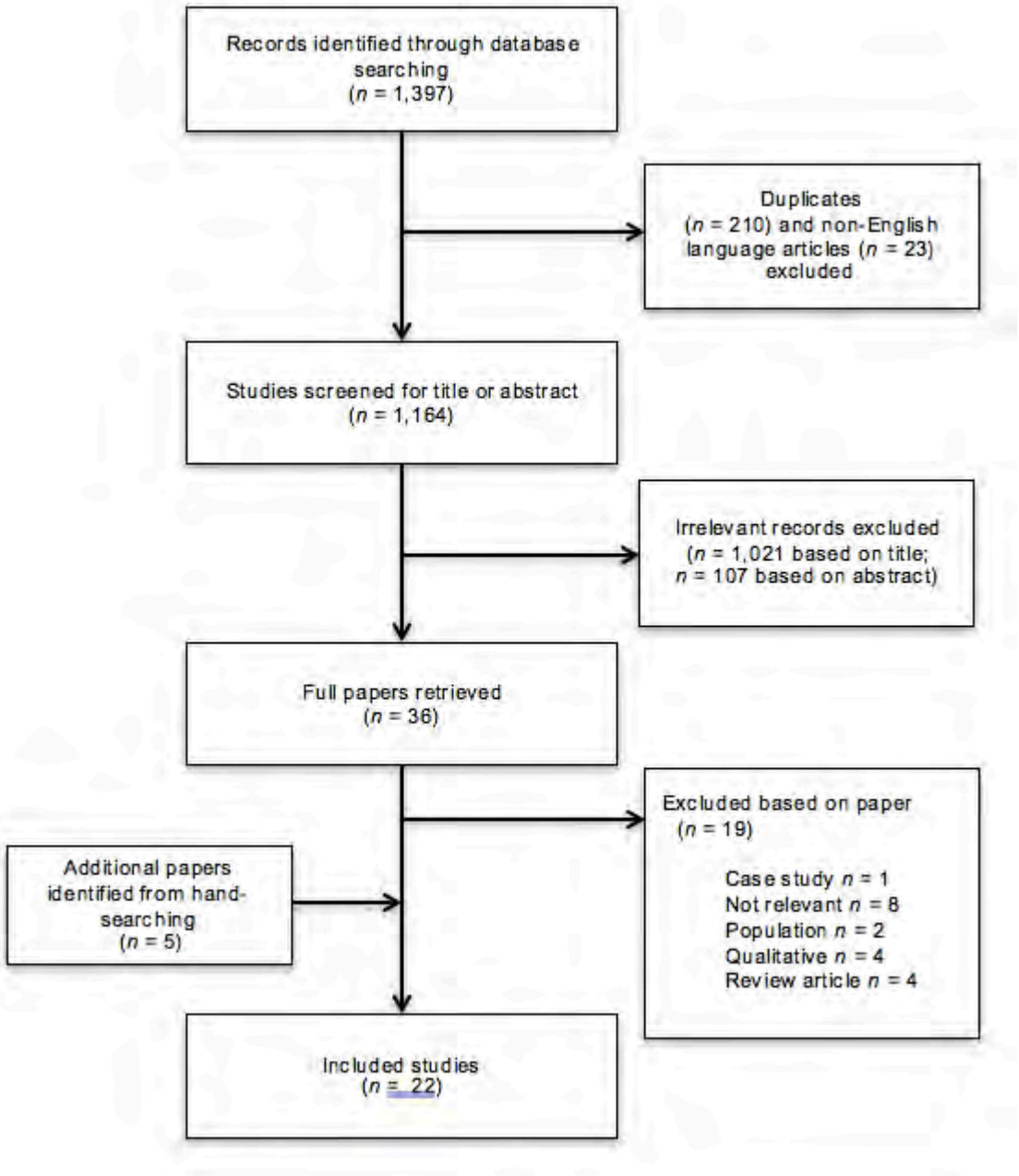

Figure 11 PRISMA flow diagram of study selection process

3.2.1 Identification of eligible studies

Electronic databases were searched to identify relevant peer-reviewed articles published between January 1946 and June (3rd week) 2015. Replicating the search strategy

reported by Clark et al. (Clark et al., 2014), the following Boolean search query was used: (opioid OR opiate) AND overdose AND prevention (see Table 5 for search protocol).

Electronic database searching generated 1,397 records: 150 on Medline, 772 on PsycINFO (both via OVID), and 475 on PubMed. Five studies (Bennett & Holloway, 2012; Lopez-Gaston et al., 2009; McAuley et al., 2010; Seal et al., 2005; Strang, Manning, Mayet, Best, et al., 2008) were added after manually searching the reference lists of recent literature reviews (Clark et al., 2014; EMCDDA, 2015; Mueller, Walley, Calcaterra, Glanz, & Binswanger, 2015).

Original quantitative (or mixed-method) studies of randomized or observational trials of THN programs that trained opioid users in overdose prevention AND reported on overdose outcomes were included in the study. Several exclusion criteria were applied: reporting on buprenorphine/ naloxone; case reports; not reporting primary research data; not reporting on heroin/opioid users, naloxone, or overdose (see Table 11 for a list of excluded studies).

Under guidance of my first supervisor, I extracted data using the STROBE-checklist (Von Elm et al., 2007), assessed study eligibility, and conducted quality appraisal using an eight-item scale (Jinks, Cotton, & Rylance, 2011), which had previously been applied by Clark et al. (2014) (see Table 9).

All 22 studies that met the inclusion criteria were entered into the analysis. Among these, one was an interrupted-time series analysis that provided quasi-experimental data. Sixteen were pre-post studies (nine with systematic follow-up), three were case-series, and two were cross-sectional. None of the studies involved randomization to the intervention (i.e. THN distribution), although two studies were controlled (Bennett & Holloway, 2012; Walley, Xuan, et al., 2013). Of the 22 included studies, 15 were carried out in the US, two in Canada, four in the UK, and one in the UK and Germany (multi-site). Sample sizes varied from a minimum of n=24 to a maximum of n=2,912 (median: n=203).

Table 5 Search protocol

Research question	**Are take-home naloxone programs effective at reducing overdose deaths among opioid users?** Aim 1: To assess the impact of take-home naloxone provision on overdose-related mortality in opioid users.
Sub-questions	**Do take-home naloxone programs lead to adverse events among opioid users?** Aim 2: To assess the safety of take-home naloxone provision among opioid users
Search strategy	**Electronic Databases:** Medline, PsycINFO (both accessed via OVID SP), and PubMed to identify relevant peer-reviewed articles published in English language between January 1946 and June (3rd week) 2015. <u>Medline:</u> 1. (opioid or opiate).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] 2. prevention.mp. 3. Drug Overdose/ or overdose.mp. 4. 1 and 2 and 3 <u>PubMed:</u> (((opioid) OR opiate) AND prevention) AND overdose <u>PsycINFO:</u> 1. opioid.mp. or exp Opiates/ 2. overdose.mp./or exp Naloxone/ or exp Drug Therapy/ or exp Drugs/ or or exp Drug Abuse/ or exp Heroin/ or exp Opiates/ or exp Drug Overdoses/ or exp Methadone/ 3. prevention.mp. or exp Prevention/ 4. 1 and 2 and 3 **Web:** UK Advisory Council on the Misuse of Drugs Public Health England US National Institute on Drug Abuse European Monitoring Centre for Drugs and Drug Addiction databases of United Nations agencies **Hand-searching (snowballing method):** Reference lists of recent literature reviews (Clark et al., 2014; EMCDDA, 2015; Mueller et al., 2015); ToC for key journals (Addiction, BMJ, Journal of Urban Health, Harm Reduction Journal).
Existing systematic reviews	Clark AK, Wilder CM, Winstanley EL. A systematic review of community opioid overdose prevention and naloxone distribution programs. Journal of Addiction Medicine. 2014;8(3):153-63. EMCDDA. Preventing fatal overdoses: a systematic review of the effectiveness of take-home naloxone. 2015.

General search filter used	Identify records from title, abstract, keywords; Map term to Medical Subject Heading Publication Year: 1946 – Current Duplicate articles to be removed using EndNote software version X6 for Windows.
Question specific search filter	(none)
Amendments to filter/ search strategy	(none)
Search Date	1 January 1946 to June (3rd week) 2015
Eligibility criteria	
• Population	Opioid users (any treatment status)
• Intervention	Take-home naloxone
• Comparison	Standard care (no take-home naloxone)
• Outcomes	Adverse reactions Deaths Follow-up Inappropriate naloxone administration (e.g. cocaine intoxication) Survived after take-home naloxone administration Take-home naloxone kits distributed Take-home naloxone kits used Unknown outcomes Secondary outcomes (not specified)
• Study design	Randomized clinical trials (RCTs) and observational studies (quantitative or mixed-method studies)
• Publication status	Original studies published in peer-reviewed journals
Exclusion criteria	Case reports Qualitative studies Reporting on naloxone/ buprenorphine Indication: not reporting on heroin or opioid users, e.g. use of naloxone to treat: - dysmenorrhea (ICD-10 N94.4-94.6; naloxone used to treat uterine contractions) - restless legs syndrome (ICD-10 G25.8) - chronic pain condition (e.g. in cancer patients) - opioid-induced bowel dysfunction Not reporting on naloxone Not reporting on overdose Not reporting primary research data
Quality assessment	Eight-item checklist (Jinks et al., 2011) The eight items are each dichotomised to 'yes' (1 point) or 'no' (0 points) and address the relevance of the study aims, appropriateness of methods used, transparency of data analysis and results, and soundness of interpretive approach.
Analysis method	Narrative synthesis by means of the Bradford Hill criteria (1965)

3.2.2 Analysis

Meta-analysis was dismissed for two reasons. Firstly, there was large variability in the size and quality of the THN intervention studies identified: many were merely descriptive reports. While valuable communications to other practitioners, these reports nevertheless lacked study design and analytical rigor. Secondly, while nine studies involved systematic follow-up, they were not considered necessarily representative of the majority of included studies due to small sample sizes. For instance, in the Seal et al. (2005) study with systematic follow-up, the 24 program participants received an 8-hour training in overdose prevention, naloxone use and cardiopulmonary resuscitation, whereas training sessions in the Massachusetts take-home naloxone program (n = 2,912) could be as short as 10 minutes (Walley, Xuan, et al., 2013). A meta-analysis of THN programs by Giglio, Li, and DiMaggio (2015) illustrates this dilemma. As central outcomes, the authors presented the mean difference in overdose prevention training scores and odds ratios of recovery from drug overdose associated with naloxone administration by bystanders. However, the authors were only able to determine odds ratios of recovery for a total of four studies (Galea, Nandi, et al., 2006; Lankenau et al., 2013; McAuley et al., 2010; Strang, Manning, Mayet, Best, et al., 2008) across which no more than 66 overdose events and 39 naloxone administrations had been reported. This number of naloxone administrations is negligible compared to the 2,336 naloxone administrations reported across 17 studies in this systematic review (i.e. excluding 4 studies which may have contained duplicate samples) (see Table 8).

Therefore, narrative synthesis was chosen as the more appropriate method of analysis in lieu of meta-analysis. In this context, the evidence was evaluated using the Bradford Hill criteria (Hill, 1965).

The Bradford Hill criteria

The Bradford Hill criteria (Hill, 1965) are a set of nine criteria (see Table 7) devised in 1965 by British epidemiologist and statistician Sir Austin Bradford Hill (see Figure 12) to assess causality when only correlational data are available: 1) Strength of Association, 2) Consistency, 3) Specificity, 4) Temporality, 5) Dose-response Relationship, 6) Plausibility, 7) Coherence, 8) Experimental Evidence, and 9) Analogy. The Bradford Hill criteria are considered a standard tool to assess the impact of broad-based public health interventions where it is ethically not feasible or operationally impractical to conduct RCTs.

Figure 12 Sir Austin Bradford Hill (1897-1991)[10]

Sir Austin Bradford Hill originally applied the criteria to the example of lung cancer related to smoking (Hill, 1965). The criteria have since been applied to a wide range of indications, from data integration in epigenetics and molecular epidemiology (Fedak, Bernal, Capshaw, & Gross, 2015) to regional public health emergencies, for instance the association between the outbreak of the Zika virus and microcephaly in Brazil (Frank, Faber, & Stark, 2016).

Within addictions research, the Bradford Hill criteria have been valuably applied in a WHO "Evidence for Action" report (authored by Dr. Alex Wodak and Annie Cooney) (WHO, 2004) on the effectiveness of needle-exchange interventions in reducing HIV among IDUs. The WHO report also considered evidence according to five additional criteria relating to feasibility and implementation (see Table 6), which are included as supplementary analysis: 10) Cost-effectiveness; 11) Absence of Negative Consequences; 12) Feasibility of Implementation, Expansion, and Coverage; 13) Unanticipated Benefits; 14) Special Populations.

Where summary outcome measures (e.g. number of naloxone administrations, overdose reversals, adverse events) were calculated across studies, I have sought to avoid (partial) duplication of samples by including only the study with the largest participant sample per project (Wagner et al., 2010; Walley, Xuan, et al., 2013) for THN projects that had produced more than one published study (i.e. Boston/Massachusetts, Los Angeles, New York, San Francisco). Vice versa, if the time periods covered by multiple studies from the same project could be clearly distinguished and did not overlap, all project evaluations entered analysis (Enteen et al., 2010; Galea, Worthington, et al.,

[10] Source: Wikipedia.org

2006; Piper et al., 2008; Rowe et al., 2015). All summary statistics are pooled, unweighted estimates from the referenced studies. The number of overdose reversals is used as proxy for the impact of THN provision on opioid overdose mortality (Aim 1), as a ratio of one fatal overdose in every 20 overdose events has been described in the literature (Darke et al., 2003), and it is impossible to ascertain for each overdose event whether, in the absence of intervention, the outcome would have been fatal or whether respiratory function would have recovered.

3.3 Results

I now present the findings from application of the nine original Bradford Hill criteria (Hill, 1965), followed by consideration of the extra five criteria added in the WHO report (WHO, 2004; Wodak & Cooney, 2006) (see Table 6).

Table 6 Additional feasibility and implementation criteria

Criterion	Take-home Naloxone (THN)
Cost-effectiveness	Is THN for lay overdose reversal cost-effective compared to treatment as usual (no intervention)?
Absence of Negative Consequences	Does the distribution of THN to users bear the risk of adverse events?
Feasibility of Implementation, Expansion, and Coverage	Is it feasible to introduce THN distribution in diverse settings, including resource-poor settings, and scale up implementation?
Unanticipated Benefits	Does the distribution of THN to users lead to unanticipated benefits?
Special Populations	How successful are THN programs in reaching special populations that have been identified as particularly “at risk” opioid users?

3.3.1 Consideration according to the original Bradford Hill criteria

1) Strength of Association

In 21 of the 22 studies, pre-provision of naloxone was followed by use of the naloxone to reverse opioid overdose. After exclusion of four studies that possibly contained duplicate samples (Doe-Simkins et al., 2009; Dwyer et al., 2015; Lankenau et al., 2013; Walley, Doe-Simkins, et al., 2013), a total of 2,336 THN administrations were found

across 17 studies (see Table 8). Due the binary outcome (survival/death), the number of successful overdose reversals can be estimated by deducting the number of deaths from the number of THN administrations. By deducting the 20 confirmed deaths (1+1+2+6+10) where overdose victims did not recover following naloxone administration (Bennett, Bell, Tomedi, Hulsey, & Kral, 2011; Bennett & Holloway, 2012; Enteen et al., 2010; Maxwell et al., 2006; Rowe et al., 2015), an upper estimate of 2,316 successful overdose reversals[11] emerges. If the four deaths where it was unclear if naloxone had been administered (Wagner et al., 2010) and 63 cases (8+36+14+5) of naloxone administration with 'unknown outcome' (Bennett et al., 2011; Enteen et al., 2010; Piper et al., 2008; Wagner et al., 2010) are also counted towards fatalities following naloxone administration, a conservative, lower estimate of 2,249 successful overdose reversals[12] emerges. In the only study where THN provision did not lead to overdose reversals (Lopez-Gaston et al., 2009), nine out of 46 program participants witnessed a total of 16 overdoses at six-month follow-up, but none administered naloxone to the overdose victims.

The main reason for non-administration was that participants did not have their naloxone supply available.

In summary, there is a strong association between THN programs and overdose survival, as evidenced by at least 2,249 successful overdose reversals (96.3%; 95% CI: 95.5, 97.1) among 2,336 THN administrations.

2) Temporality

In 21 of the 22 studies, training in overdose prevention and THN provision preceded overdose reversals. Two of these studies provide clear evidence in support of the temporality criterion. Supportive evidence comes from descriptive accounts of early THN distribution in Chicago and surrounding Cooks County (Maxwell et al., 2006): after a 135% increase in local overdose deaths from 1996-2000, the introduction of THN in 2001 led to reduction in fatal overdoses by 20% in 2001, 8% in 2002, and 6% in 2003 (compared to past-year rate). While these data are indicative of a temporal sequence between THN introduction and reduced overdose mortality, no definite conclusion can

[11] 2,316 OD reversals equals 2,336 THN administrations minus 20 deaths

[12] 2,249 OD reversals equals 2,336 THN administrations minus 20 deaths minus 4 unclear cases minus 63 cases with unknown outcome

be drawn, as the lack of control group means that other causes may have contributed to decreasing overdose mortality rates.

Stronger evidence comes from Walley, Xuan et al. (2013) who conducted an evaluation of a state-funded THN program in Massachusetts. Between 2006 and 2009, the Massachusetts Department of Public Health used a phased roll-out to introduce THN in 19 communities, enrolling 2,912 individuals in total. To evaluate the impact of THN, Walley, Xuan et al. (2013) used an interrupted time-series analysis, where each community served as its own geographic control and communities without concurrent THN availability served as time control. For all 19 participating communities, overdose mortality rates in the time periods before and after THN implementation were compared. Overdose mortality rates were significantly reduced in communities where THN was implemented - compared to pre-implementation rates and to communities without THN.

3) Consistency

Overdose reversals by means of THN have been documented in the selected studies by independent investigators under different circumstances in at least 15 different cities, states and countries: in Canada (Toronto & British Columbia), the USA (Baltimore, Boston/Massachusetts, Chicago, Los Angeles, San Francisco, New York, Pittsburgh, Rhode Island), the UK (England, Jersey, Scotland, Wales), and Germany (Berlin). Overdose reversals by THN have also been documented repeatedly in New York (Galea, Worthington, et al., 2006; Piper et al., 2008) and San Francisco (Enteen et al., 2010; Rowe et al., 2015; Seal et al., 2005). In conclusion, there is substantial support for the consistency criterion.

4) Biological Plausibility

This criterion addresses the therapeutic effect of naloxone. Naloxone is a pure opioid antagonist that binds to the μ-opioid receptor and blocks competing agonists, such as heroin (NIH, 2007). All but one study (Lopez-Gaston et al., 2009) reported on THN administration in cases of suspected opioid overdoses, and the pharmacological effects of naloxone led to at least 2,249 overdose reversals. In conclusion, there is strong empirical support to the biological plausibility criterion.

5) Coherence

Declining overdose rates in the absence of THN have been reported in the literature. The Australian heroin drought constitutes a prominent example, where overdose-related mortality rates dropped between 2001 and 2002 in conjunction with a shortage in illicit heroin imports. THN could not have accounted for the decline in mortality, as it was only introduced in Australia in 2011 (ACT-Health, 2014; Degenhardt, Day, Gilmour, & Hall, 2006). However, the Australian example does not conflict with the presumed effect of THN on reduced overdose mortality. The cause-and-effect interpretation of our data is consistent with current understanding of the mechanisms of opioid overdose, and the 21 studies which reported overdose reversals provide strong support for the coherence criterion.

6) Specificity

The Specificity criterion relates to efficacy of the intervention (same as Biological Plausibility), rather than population-wide effectiveness. THN exclusively reverses opioid-induced overdoses, as illustrated by the following two cases: in the Dettmer et al. study (Dettmer et al., 2001), naloxone had zero effect when administered to a person suffering from cocaine intoxication. The Chicago Recovery Alliance reported one fatality after naloxone administration (Maxwell et al., 2006) where naloxone failed to revive an overdose victim with non-opioids in their system. The mooted benefit from naloxone is specific to opioid overdose. In practice, THN may be primarily beneficial for the reversal of overdoses from heroin and other short-acting opioids. (All 22 studies reported primarily on heroin overdoses, and one study specified that the long-acting opioid methadone was involved in less than 5% of overdose reversals (Walley, Doe-Simkins, et al., 2013)). Overall, the evidence constitutes strong support for this criterion.

7) Dose-response Relationship

Researchers estimate that THN distribution can only achieve maximum impact on overdose reduction if a certain volume of THN kits is available in the community. Among the 22 studies, only Walley, Xuan et al. (2013) assessed the impact of varying degrees of THN availability on overdose mortality by splitting the 19 participating communities into three groups based on volume of THN distribution: zero implementation, low implementation (1-100 program enrollments per 100,000 inhabitants), and high implementation (>100 enrollments). Both low and high implementers had significantly reduced overdose mortality rates compared to communities without implementation, and

there was a significant implementation dose-relationship with overdose death rates, with greatest effect with greatest implementation. To summarize, there is only this limited empirical evidence for a dose-related impact of THN availability, and hence this criterion is only partially fulfilled.

8) Experimental Evidence

While none of the 22 studies deliver experimental evidence, the interrupted time-series analysis by Walley, Xuan et al. (2013) provides quasi-experimental evidence in support of causation. Importantly, even communities with low-level THN implementation of THN (1-100 participants, see above) saw a reduction in overdose mortality, compared to communities without THN distribution. Interrupted time-series analysis is considered to be the strongest quasi-experimental research design (Penfold & Zhang, 2013). The results of the study by Walley, Xuan et al. (2013) thus provide preliminary support for the Experimental Evidence criterion.

9) Analogy

THN is analogous to naloxone treatment for the same clinical indication in emergency medical care, and also to the prescription of other emergency medications (typically antidotes for overdose or poisoning) for peer administration: THN has been compared to the provision of adrenaline injection kits (e.g., EpiPen) to individuals with severe allergic reactions for family members to administer in the event of anaphylactic shock (Strang, Manning, Mayet, Best, et al., 2008) or the provision of glucagon for insulin overdose (Maxwell et al., 2006). Similarly, THN has been likened to pre-placement of defibrillators and CPR training for lay people likely to witness cardiac arrest (Wagner et al., 2014). For all these emergency interventions, timely delivery is crucial. The analogy criterion is therefore fulfilled.

Table 7 Bradford Hill criteria: definition and application to take-home naloxone

Criterion	Definition	Take-home naloxone (THN)
Strength of Association	The stronger the association between the exposure to a treatment and the clinical outcome, the less likely it is influenced by an external variable.	How strong is the association between THN and OD reversal?
Temporality	A cause-and-effect hypothesis can only find empirical support if the presumed cause precedes the effect in time.	Did the distribution of THN precede a reduction in OD deaths?
Consistency	The credibility of a finding increases if different investigators can replicate it across different locations and under different circumstances.	Have there been multiple observations of OD reversals as a result of THN provision?
Biological Plausibility	There is stronger support for causality if there is a likely biological or pharmacological mechanism that can explain the association between exposure to a treatment and the outcome.	Is it biologically plausible that a reduction in OD deaths occurs when THN is available?
Coherence	Causality between a treatment and outcome is supported when the association is coherent with current knowledge of the disease. Vice versa, conflicting or lack of supporting evidence would count against coherence.	Are there documented examples of opioid OD mortality declining without THN availability? If so, does this empirical evidence conflict with the assumed association between THN and OD prevention?
Specificity	Causality can be established when one intervention leads to one specific outcome.	Does THN have the unique effect of reversing opioid ODs?
Dose-Response Relationship	If a dose-response relationship can be observed for the cause-and-effect hypothesis, increased exposure to treatment will proportionally impact the clinical outcome.	Does increased THN supply go hand-in-hand with more OD reversals?
Experimental Evidence	If experimental manipulation of the exposure-outcome association impacts the outcome, (semi) experimental evidence is given. This delivers the strongest support for causation.	Is there (semi-) experimental evidence to support the hypothesized impact of THN on OD mortality?
Analogy	If a treatment/exposure factor similar to A leads to a clinical outcome similar to B, then this analogy counts as evidence in support of our hypothesis that A causes B.	Is there a treatment similar to THN that leads to an outcome similar to OD reversal?

3.3.2 Consideration according to additional feasibility and implementation criteria

10) Cost-effectiveness

Separate modelling data from both the U.S. and Russia conclude that THN is cost-effective even under conservative circumstances, i.e. when the cost of naloxone increases and the rate of observed overdoses decreases (Coffin & Sullivan, 2013a, 2013b). Bearing in mind the potential limitation that both studies were conducted by the same authors, there is consistent evidence for the cost-effectiveness of THN.

11) Absence of Negative Consequences

In five of the 17 studies that did not contain duplicate samples, 20 overdose victims did not survive naloxone administration (Bennett et al., 2011; Bennett & Holloway, 2012; Enteen et al., 2010; Maxwell et al., 2006; Rowe et al., 2015). In addition, Wagner et al. (2010) reported four deaths where it was unclear if naloxone had been administered. Based on these observations, the following fatality rates emerge: 20 confirmed deaths per 2,336 naloxone administrations (0.9%; 95% CI: 0.5, 1.2), or 24 deaths per 2,336 naloxone administrations (1.0%; 95% CI: 0.6, 1.4) if the four fatalities are included where it was unclear if naloxone had been administered. If the study selection is limited to the nine articles with systematic follow-up, a similar ratio of one confirmed death per 123 naloxone administrations (0.8%; 95% CI: 0.4, 1.2) was observed.

In six (Dettmer et al., 2001; Enteen et al., 2010; Maxwell et al., 2006; Strang, Manning, Mayet, Best, et al., 2008; Tzemis, Al-Qutub, Amlani, Kesselring, & Buxton, 2014; Wagner et al., 2010) of the 17 studies, several adverse reactions were reported in conjunction with a total of 2,336 naloxone administrations: at least 65 instances of withdrawal symptoms (2.8%), 52 cases of vomiting (2.2%), 50 cases of agitation (2.1%), and four seizures (0.1%).

In conclusion, THN programs have a low rate of adverse events. Where adverse reactions occurred, these were most frequently symptoms of opioid withdrawal (incl. nausea/vomiting, agitation).

12) Feasibility of Implementation, Expansion, and Coverage

The 22 studies document THN implementation in a variety of settings across 16 geographical locations, and naloxone usage rates between 5%-63% are reported. San

Francisco is an example of rapid expansion, as the volume of THN kits distributed increased from 24 in 2001 to 2,962 kits over the six-year period between 2003-2009 (i.e. approximately 494 kits/year) (Enteen et al., 2010), and to 2,500 kits from 2010 to 2013 (i.e. approximately 833 kits/year) (Rowe et al., 2015). Outside of the 22 studies included in this review, implementation in resource-poor settings has been achieved in Kyrgyzstan and Tajikistan, with reported naloxone usage rates of 47% and 78%, respectively (Kan et al., 2014). These studies suggest that THN schemes are capable of implementation across a wide range of settings and cultures.

13) Unanticipated Benefits

Four of the 22 studies reported unanticipated benefits. In THN programs in California, 25% of participants in San Francisco entered treatment within 6-month follow-up (Seal et al., 2005), and 53% of participants in Los Angeles reported decreased drug use at 3-month follow-up (Wagner et al., 2010). Similarly, Maxwell et al. reported anecdotal evidence of increased willingness among THN recipients to be tested for HIV and HCV (Maxwell et al., 2006). Strang et al. (2008) found a secondary training effect: within a 3-month follow-up period, 28% of THN recipients had trained a family member or peer.

14) Special Populations

THN provision has successfully been implemented in programs targeting special populations with high risk of overdose: detox patients (Lopez-Gaston et al., 2009; Walley, Doe-Simkins, et al., 2013), homeless users (Enteen et al., 2010; Piper et al., 2008; Rowe et al., 2015; Wagner et al., 2010; Yokell, Green, Bowman, McKenzie, & Rich, 2011), methadone patients (Walley, Doe-Simkins, et al., 2013) and prison inmates (Bennett & Holloway, 2012). The Massachusetts THN program (Walley, Xuan et al., 2013) also enrolled attendees of HIV education centers, and a Los Angeles-based program recruited over 50% HCV-positive patients. Both represent particularly vulnerable groups due to their comorbid health issues and risk of blood-borne virus transmission by needle-sharing. From the perspective of implementation, THN schemes can be delivered to populations in special need.

Table 8 THN kits distributed and used, overdose reversals, and adverse events

Study	n	THN kits distributed	THN kits used (%)	Deaths	OD Reversal after THN**	Unknown Outcomes	Adverse Reactions
Bennett 2011	426	426	249 (58%)	2	≥ 96%	8	NR
Bennet 2012	525	NR	28 (NR)	1	96%		NR
Dettmer 2001a	101	101	5 (5%)	0	100%		Withdrawal (NR)
Dettmer 2001b	124	124	29 (23%)	0	100%		Withdrawal (10)
Doe-Simkins 2009*	385	385	74 (19%)	0	100%		Withdrawal (2)
Dwyer 2015*	415	56	6 (11%)	0	100%		NR
Enteen 2010	1,942	2,962	399 (13%)	6	≥ 89%	36	Vomiting (50), Agitation (36), Seizures (3)
Galea 2006	25	25	10 (40%)	1[a]	100%	1[a]	None
Lankenau 2013*	30	30	15 (50%)	0	≥ 97%	1	NR
Leece 2013	209	209	17 (8%)	0	100%		None
Lopez-Gaston 2009	70	70	0 (0%)	1[a]	N/A		N/A
Markham Piper 2008	122	122	82 (67%)	0	≥ 83%	14	NR
Maxwell 2006	1,120	3,500	319 (9%)	1[c]	99%		Seizures (1), Vomiting (1)
McAuley 2010	41	19	2 (11%)	1[a]	100%		NR
Rowe 2015	2,500	2,500	702 (28%)	10	99%		NR
Seal 2005	24	24	15 (63%)	0	100%		NR
Strang 2008	239	239	1 (5%)	1[a]	100%		Withdrawal
Tobin 2009	250	250	22 (9%)	0	100%		NR
Tzemis 2014	692	836	85 (10%)	0	100%		Withdrawal (55), Agitation (9)
Wagner 2009	66	66	28 (42%)	4[b]	NR	5	Agitation (5), Vomiting (1)
Walley, Xuan 2013	2,912	2,912	327 (11%)	0	100%		NR
Walley, Doe-Simk. 2013*	1,553	1,553	92 (6%)	0	100%		NR
Yokell 2011	120	120	5 (4%)	0	100%		NR

Annotations: [a] naloxone not administered; [b] unclear if naloxone administered; [c] non-opioids present; N/A: not applicable; NR: not reported; THN: take-home naloxone; * not included in summary measures to avoid (partial) duplication of samples; ** where applicable, unknown outcomes were counted towards unsuccessful THN administrations (as indicated by the '≥' sign).

Table 9 Included Studies: Follow-up rate, study design, and quality rating

Study	Location	n	FU	FU %	FU Type	Design	Score
Bennett 2011	Pittsburg	426	89	21%	non-systematic	pre-post	5
Bennet 2012	Wales	525	28	5%	systematic	pre-post	6
Dettmer 2001a	Jersey	101	NR	NR	non-systematic	case series	4
Dettmer 2001b	Berlin	124	40	32%	non-systematic	case series	4
Doe-Simkins 2009	Boston	385	278	72%	non-systematic	pre-post	5
Dwyer 2015	Boston	415	51	12%	systematic	pre-post	6
Enteen 2010	San Francisco	1,942	310	16%	non-systematic	pre-post	6
Galea 2006	New York	25	22	88%	systematic	pre-post	7
Lankenau 2013	Los Angeles	30	N/A	N/A	N/A	cross-sectional	6
Leece 2013	Toronto	209	NR	NR	non-systematic	case series	5
Lopez-Gaston 2009	Birmingham & London	70	46	65%	systematic	pre-post	7
Markham Piper 2008	New York	122	NR	NR	non-systematic	pre-post	6
Maxwell 2006	Chicago	1,120	NR	NR	non-systematic	case series	4
McAuley 2010	Lanarkshire	41	17	89%	systematic	pre-post	7
Rowe 2015	San Francisco	2,500	613	25%	non-systematic	pre-post	7
Seal 2005	San Francisco	24	24	100%	systematic	pre-post	5
Strang 2008	England	239	186	78%	systematic	pre-post	7
Tobin 2009	Baltimore	250	85	34%	systematic	pre-post	6
Tzemis 2014	British Columbia	692	N/A	N/A	N/A	cross-sectional	6
Wagner 2009	Los Angeles	66	47	71%	systematic	pre-post	7
Walley, Xuan 2013	Massachusetts	2,912	212	7%	non-systematic	ITS	7
Walley, Doe-Simk. 2013	Massachusetts	1,553	286	18%	non-systematic	pre-post	6
Yokell 2011	Rhode Island	120	10	8%	non-systematic	pre-post	5

Annotations: FU: number of follow-up participants; FU%: FU participants as percentage of study sample; ITS: interrupted time-series analysis; N/A: not applicable; NR: not reported; Score: summary quality score based on 8-point scale by Jinks et al. (Jinks et al., 2011), modified from Clark et al. (Clark et al., 2014).

Table 10 Studies cited in support of 9 Bradford Hill and 5 WHO criteria

	BRADFORD HILL CRITERIA									WHO CRITERIA				
STUDY	Strength of Association	Temporality	Consistency	Biological Plausibility	Coherence	Specificity	Dose-Response	Experimental Evidence	Analogy**	Cost-effectiveness	Absence of Negative Consequences	Feasibility	Unanticipated Benefits	Special Populations
Bennett 2011	✓		✓	✓	✓						†	✓		
Bennet 2012	✓		✓	✓	✓						†	✓		✓
Dettmer 2001a	✓		✓	✓	✓	✓					AR	✓		
Dettmer 2001b	✓		✓	✓	✓	✓					AR	✓		
Doe-Simkins 2009	✓		✓	✓	✓							✓		
Dwyer 2015	✓		✓	✓	✓							✓		
Enteen 2010	✓		✓	✓	✓						AR,†	✓		✓
Galea 2006	✓		✓	✓	✓							✓		
Lankenau 2013	✓		✓	✓	✓							✓		
Leece 2013	✓		✓	✓	✓							✓		
Lopez-Gaston 2009*												✓		✓
Markham Piper 2008	✓		✓	✓	✓							✓		✓
Maxwell 2006	✓	✓	✓	✓	✓	✓					AR,†	✓	✓	
McAuley 2010	✓		✓	✓	✓							✓		
Rowe 2015	✓		✓	✓	✓							✓		✓
Seal 2005	✓		✓	✓	✓							✓	✓	
Strang 2008	✓		✓	✓	✓						AR	✓	✓	
Tobin 2009	✓		✓	✓	✓							✓		
Tzemis 2014	✓		✓	✓	✓						AR	✓		
Wagner 2009	✓		✓	✓	✓						AR,†	✓	✓	✓
Walley, Xuan, 2013	✓	✓	✓	✓	✓		✓	✓				✓		
Walley, Doe-Simk. 2013	✓		✓	✓	✓	✓						✓		✓
Yokell 2011	✓		✓	✓	✓							✓		✓
Coffin 2013a										✓				
Coffin 2013b										✓				
Kan 2014												✓		

Annotations: ✓ study cited in support of criterion; * Lopez-Gaston et al. (2009) reported no THN administrations; ** None of the studies explicitly examined the Analogy criterion and have not been ticked (by definition, this criterion requires reasoning by analogy); † cited for reporting fatal OD outcome(s) following THN administration; AR: cited for reporting adverse reaction(s) following THN administration.

3.4 Discussion

3.4.1 Statement of principal findings

Empirical evidence from the 22 studies reporting on THN interventions for opioid users meets all nine Bradford Hill original criteria. Among these, Sir Austin Bradford Hill considered the Experimental Evidence criterion to deliver the strongest support for causation (Hill, 1965), but only quasi-experimental evidence from one study (Walley, Xuan et al., 2013) is available here. The robustness of empirical support ranges from one study per criterion (Dose-Response, Experimental Evidence) to 21 studies per criterion (Strength of Association, Coherence) (see Table 10). With regard to the five additional criteria assessing feasibility and implementation, THN fully or partially fulfils all five criteria. It is found to be cost-effective, and existing projects were able to access and train high-risk populations that led to 2,336 layperson naloxone administrations (Aim 1) with a low rate of adverse effects (Aim 2).

I conclude that, on the basis of application of the Bradford Hill criteria to the current evidence base on THN, there is strong support for the causation hypothesis. While the evidence is sometimes based on only one or two studies, I nevertheless conclude that this constitutes support for all nine criteria. THN provision reduced fatal outcome of overdose among program participants themselves, among fellow opioid users, and in the wider community, as evidenced by public vital statistics records (Seal et al., 2005; Walley, Xuan et al., 2013). Alternative explanations for this observation are unlikely: in control communities that did not implement THN, opioid overdose mortality was significantly higher (Walley, Xuan et al., 2013). The risk associated with THN programs is relatively low, especially when the life-threatening nature of the emergency situation is borne in mind: in studies with systematic follow-up, one death was reported among 123 overdose victims who were administered THN. Moreover, there is no empirical evidence to support the concern that THN programs might encourage heroin use. Two studies reported decreased drug use among THN program participants at follow-up (Seal et al., 2005; Wagner et al., 2010), whereas a more recent study found no overall change in the frequency of heroin use across THN recipients (Doe-Simkins et al., 2014).

3.4.2 Strengths and weaknesses of the chapter

This is the first published application of the Bradford Hill criteria to assess the international evidence base on THN. Our findings extend and substantiate the 2014 WHO Guidelines as well as the results of the previous systematic reviews by Clark et al. (2014) and the EMCDDA (2015). Clark et al. (2014) cautiously concluded *"participation [in THN programs] is associated with overdose reversals"* (p. 162) but avoided

statements on the effectiveness of THN, whereas the EMCDDA stated *"there is evidence that educational and training interventions with provision of take-home naloxone decrease overdose-related mortality"* (p. 11).

There are potential limitations to this analysis, which need to be borne in mind. Selection bias may have affected the internal validity of the data included. Among 19 studies with pre-post and case series designs, 10 relied on unsystematic follow-up to capture overdose events and naloxone usage; relying on spontaneous follow-up, with THN program participants typically asked to report back on naloxone usage when collecting a naloxone refill. This raises scientific analytical doubt about data quality and interpretations: first of all, across these 10 studies, less than a quarter (22.9%; i.e. 1,973/8,602) of THN recipients returned for refills after THN use, and information on the majority of participants was consequently lost. Secondly, it is possible that users with positive naloxone experiences (e.g. successful overdose reversals) may be more likely to return for a refill of their THN kit and complete a follow-up survey, whereas those with negative naloxone experiences may not be captured in the follow-up. The lack of systematic follow-up in the majority of studies is reflected in the wide range of follow-up rates attained across all studies (min. 5%, max. 100%). High levels of dropout can reduce the external validity and generalizability of results. A further source of potential bias lies in the fact that, for 21 out of the 22 studies, there was an exclusive reliance on self-report data for overdose outcomes. Only the interrupted time-series analysis by Walley, Xuan et al. (2013) included a public database of vital statistics to calculate overdose fatality rates. A further limitation concerns the fact that the Experimental Evidence and Dose-Response criteria hinge on data from the Walley, Xuan et al. (2013) study.

3.4.3 Possible mechanisms and implications for clinicians

With regard to clinical implications, it needs to be emphasized that the vast majority of studies included in this review reported on heroin overdoses. Consequently, the generalizability of my findings to overdoses from long-acting opioids is unclear. Even when methadone patients were specifically recruited into a THN program (Walley, Doe-Simkins, et al., 2013), over 90% of witnessed (and reversed) overdoses were heroin-induced. The results of this review on the effectiveness of THN are thus limited to impact on heroin overdoses, and the effectiveness of the intervention for overdoses from long-acting opioids (e.g. methadone or many prescription opioids) needs to be explored in future research.

3.4.4 Questions for future research

More robust studies are needed to confirm these results and assess their applicability to other regions internationally, in particular low- and middle-income countries. Moreover, the findings from the studies do not inform which distribution model of overdose education and THN distribution is preferable. Future studies could formally evaluate the impact of program components by providing THN to all subjects and randomizing subjects into different training conditions (e.g. 'overdose education' versus 'overdose education + CPR training').

Despite these methodological limitations, positive reports of overdose reversals following THN distribution were reported across 21 studies - regardless of type of follow-up (systematic vs. unsystematic) or data source (self-report vs. objective data), suggesting that the finding is indeed robust and not an artefact of methodological flaws.

To control for potential publication bias, I additionally searched the grey literature for documents reporting on THN initiatives that are not published in the peer-reviewed journal domain. While this search was unlikely exhaustive, the data reported in the grey literature are broadly consistent with the results of the studies included in our systematic review. For instance, in the Scottish National Naloxone Programme, in the years 2012 and 2013, the percentage of opioid-related deaths occurring within four weeks of prison release (5.5% and 4.7%) was almost half that of the pooled 2006-10 baseline indicator (9.8%), suggesting that distribution of naloxone kits on release may reduce the risk of fatal overdose among (former) prisoners with history of opioid use (ISD, 2014).

3.5 Conclusion

To conclude, application of the Bradford Hill criteria to the current evidence base from non-randomized studies finds that THN programs have led to improved survival rates among program participants and reduced heroin overdose mortality rates in the community (Aim 1) and are only accompanied by a low rate of adverse events (Aim 2). In the absence of RCTs, I conclude that THN distribution to at-risk users should be introduced as standard of care for the community-based prevention of heroin overdose deaths.

Table 11 Studies excluded after full-text review (n=19)

Study ID	DOI / URL	Search Source	Reason for exclusion
Albert et al. (2011)	10.1111/j.1526-4637.2011.01128.x	Electronic database	Population: no opioid users (refugees)
Arribas-Ibar et al. (2014)	10.1186/1477-7517-11-33	Electronic database	Not relevant (no overdose outcomes)
Bagley et al. (2015)	10.1080/08897077.2014.989352	Electronic database	Not relevant (no overdose outcomes); Population: no opioid users (family members)
Behar et al. (2015)	10.1016/j.drugalcdep.2014.12.009	Electronic database	Not relevant (no overdose outcomes)
Bird et al. (2015)	10.3109/09687637.2014.981509	Electronic database	Review article (protocol)
Bowman et al. (2008)	rimed.org/medhealthri/2008/2008-09.pdf	Electronic database	Review article
Brason et al. (2013)	classic.ncmedicaljournal.com/wp-content/uploads/2013/05/74323-Brason-Final.pdf	Electronic database	Not relevant (no numeric information on THN)
CDC (2012)	cdc.gov/mmwr/pdf/wk/mm6106.pdf	Electronic database	Review article
Dahlem et al. (2015)	10.1002/2327-6924.12249	Electronic database	Not relevant (no overdose outcomes)
Jones et al. (2014)	10.1016/j.drugpo.2013.05.006	Electronic database	Not relevant (no overdose outcomes)
Kan et al. (2014)	10.1016/j.drugpo.2014.01.005	Electronic database	Not relevant (no overdose outcomes)
Sherman et al. (2008)	10.1186/1477-7517-5-2	Electronic database	Qualitative study
Wagner et al. (2014)	10.1016/j.drugpo.2013.07.003	Electronic database	Qualitative study
Wheeler et al. (2015)	cdc.gov/mmwr/pdf/wk/mm6423.pdf	Electronic database	Review article
Wilder et al. (2014)	10.1097/ADM.0000000000000032	Electronic database	Case study
Williams et al. (2014)	10.1111/add.12360	Electronic database	Population: no opioid users (family members)
Worthington et al. (2006)	10.1186/1477-7517-3-19	Electronic database	Not relevant (no overdose outcomes), qualitative study
Wright et al. (2006)	10.1186/1747-597x-1-28	Electronic database	Qualitative study
Zaller et al. (2013)	10.3109/10826084.2013.793355	Electronic database	Qualitative study

Chapter 4 The Insufficiency of Improvised Nasal Naloxone Kits

Preface

In this chapter I raise the question whether it is acceptable for clinicians to supply unlicensed, improvised nasal naloxone kits. My idea for this chapter arose from comparison of the results of an ambulance-based randomized controlled trial in Australia (Kerr, Kelly, Dietze, Jolley, & Barger, 2009) and of naloxone refill data from the Massachusetts take-home naloxone program (Doe-Simkins et al., 2009; Walley, Xuan et al., 2013). If the Australian ambulance staff observed that about one in five patients with suspected heroin overdose needed "rescue naloxone" (i.e. a second naloxone dose, this time by injection) following administration of improvised naloxone nasal spray (2mg/mL), then how come this non-response rate was not also reported in the Massachusetts take-home naloxone programs that distributed similar improvised nasal kits (2mg/2mL)? Did the lack of systematic follow-up of the take-home naloxone recipients in Massachusetts (see also Chapter 3 Discussion) provide an incomplete picture? The content of this chapter was developed between January 2015 and January 2016 and has been published as a peer-reviewed, first-authored manuscript entitled "Clinical provision of nasal naloxone without experimental testing and without regulatory approval – imaginative shortcut or dangerous bypass of essential safety procedures?" in Addiction, in co-authorship with my first supervisor and two colleagues from the Addictions Department at King's College London, Basak Tas and Dr. Edward Day (Strang, McDonald, Tas, & Day, 2016).

The manuscript was published as a "For Debate" article. This manuscript category designates opinion pieces that "synthesize the research literature in a way that adds important new insights […] [to] challenge existing thinking" (Addiction, 2017).

The publication of my manuscript was accompanied by a press release and stirred a lively debate among international experts in the field. Researchers from Australia, the US, and Norway submitted seven commentaries in total which provided alternative opinions on the use of improvised nasal kits, and my first supervisor and I submitted two responses to the commentaries. According to the Addiction editorial office, my "For Debate" article ranks among the top 1% of most downloaded papers in the journal in the year 2016.

While this chapter highlights the issues associated with the use of improvised nasal kits without regulatory approval, alternative routes of administration for non-injectable naloxone delivery are explored in Chapter 5.

4.1 Introduction

Naloxone undoubtedly saves lives by reversing respiratory depression caused by heroin/opioid overdose. Naloxone is approved for intravenous (IV), intramuscular (IM) or subcutaneous injection for treatment of heroin/opiate overdose (WHO, 2014). The recommended initial dose for injection is 0.4mg, which may then be increased to 2mg, according to response, and may be repeated thereafter in extremis (WHO, 2014) (see Chapter 1).

Systematic reviews conclude that take-home naloxone programs are effective (Clark et al., 2014; EMCDDA, 2015; McDonald & Strang, 2016) (see Chapter 3), and recent World Health Organization guidelines (WHO, 2014) recommend that anyone likely to witness an opioid overdose should have access to the antidote. Take-home naloxone has been implemented by early adopters in at least a dozen countries, but has only become more mainstream in the past decade with the introduction of the first state-wide program in Massachusetts in 2008 (Doe-Simkins et al., 2009) and first national programs in Scotland and Wales in 2011 (Strang et al., 2014) (see Chapter 2).

As of May 2017, a variety of nasal naloxone formulations are currently in development. A first tested and approved concentrated naloxone nasal spray product (4mg/0.1mL) by Adapt Pharma (hereafter referred to as “Adapt”; NARCAN®) already exists in North America, having received regulatory approval in the US in November 2015 (FDA, 2015) and in Canada in October 2016 (CBCnews, 2016), and the arrival of a first licensed nasal spray in Europe is anticipated for late 2017 or early 2018. It is interesting to note that the concentrations of these novel formulations vary greatly, with volumes and single doses ranging from 0.1mL to 0.5mL and from 1mg to 4mg, respectively.

These recent developments can be traced back to 12 April 2012, when a step-change occurred with the joint meeting of the US FDA, Centers for Disease Control and Prevention (CDC), and National Institute on Drug Abuse (NIDA) to encourage new non-injectable naloxone formulations, alongside FDA clarification of the regulatory benchmark for no-injectable naloxone products (see Chapter 5).

Prior to the joint CDC/FDA/NIDA initiative in 2012, only one patent application (WO/2012/156317) for non-injectable naloxone containing human in-vivo data had been filed (see Chapters 6 and 7), highlighting very limited investment from pharmaceutical industry. With injectable naloxone-hydrochloride solution available as generic and off-patent medication, naloxone was of limited commercial value. Moreover, as an antidote, naloxone is only prescribed for emergency use (unlike e.g. medications for opioid substitution therapy), and its per-patient sales volume limited accordingly. When NIDA announced that it would fund development of “user-friendly” naloxone delivery systems

(Volkow et al., 2014), industry interest finally appeared.

The two pharmaceutical companies Adapt and Indivior submitted separate New Drug Applications for nasal naloxone to the US FDA in mid-2015, of which only the Adapt product (NARCAN®) was approved in November that year. Health Canada approval followed in October 2016 (CBCnews, 2016). This product delivers a concentrated nasal spray of a 4mg naloxone dose in a 0.1ml volume through a single unit-dose device by Aptar Pharma (hereafter referred to as "Aptar) for disposable use (see Figure 13) (FDA, 2015). The nasal spray has a promising pharmacokinetic profile with good bioavailability (Krieter et al., 2016) which met the FDA criteria of comparability of systemic exposure to naloxone injection (see Chapter 5 for a description of the criteria).

Figure 13 Single unit-dose device (Aptar Pharma)[13]

The New Drug Application for the competitor product by Indivior (1mg/0.1ml formulation, also in the Aptar device) was unsuccessful because the naloxone nasal spray was found not to be absorbed sufficiently rapidly relative to the reference product of 0.4mg intramuscular naloxone (Indivior, 2015). This accords with the concerns described in this chapter.

Another unsuccessful New Drug Application was submitted by a third company, Amphastar Pharmaceuticals (hereafter referred to as "Amphastar"). Amphastar already holds the U.S. license for two 2mg/2mL injectable naloxone products (Luer-Jet™ Prefilled Syringe; Min-I-Jet™ Fixed Needle Syringe) (Amphastar, 2016). The failed Amphastar naloxone nasal spray consisted of a 2mg/0.5mL dose (from 4mg/mL formulation), likely administered from a pre-filled syringe with spray device and intended to be split across the two nostrils. In February 2017, the FDA issued a Complete

[13] Source: http://news.aptar.com/solutions/aptar-pharma-provides-unit-dose-nasal-spray-technology-for-treatment-of-opioid-overdose/

Response Letter (CRL) to Amphastar, stating that the device and its usability required improvement before the New Drug Application could potentially be approved (Amphastar, 2017).

In the UK, Mundipharma Research Ltd. has recently developed a 2mg/0.1mL concentrated naloxone nasal spray (see Chapter 9) for delivery by the Aptar device and has submitted a product portfolio to the European Medicines Agency for regulatory review. The notion of nasal naloxone is unquestionably attractive for layperson use. It is quick to administer and reduces risk of needle-stick injury.

However, at the start of my PhD in October 2013, no licensed naloxone nasal spray product existed anywhere in the world. Up until late 2015, naloxone for intranasal (IN) administration was not licensed anywhere in the world – neither for addiction or overdose treatment nor for any other medical indication. Only improvised nasal naloxone kits, consisting of a pre-filled syringe (2mg/2mL) with a nasal mucosal atomizer, see Figure 14) were available, and some services (parts of the US; Norway; Denmark[14]; parts of Scotland) began to supply the improvised kits for take-home use (CDC, 2015; Greig, 2012), and they continue to be used, despite not having been formally tested for safety or efficacy.

Figure 14 Pre-filled syringe with nasal mucosal atomizer device[15]

[14] The Danish naloxone kit contains the nasal atomizer as well as a needle for injection.

[15] Source: http://www.chrisatwoodfoundation.org/naloxone

This follows a practice used by some ambulance teams that administer naloxone off-label as nasal spray (Barton et al., 2005). Off-label use generally designates the re-purposing of prescription drugs “for any indication not explicitly prohibited by law” (Doe-Simkins et al., 2009) or for unapproved age groups, dosages, or routes of administration. However, the context of emergency care is fundamentally different from emergency care from a family member or peer with a nasal spray naloxone kit. In the ambulance context, the paramedic teams can give a naloxone injection when the nasal spray fails. No fallback treatment exists in the community setting for the family member or carer with only the nasal spray. As a result, the UK Advisory Council on the Misuse of Drugs (ACMD) do not view the off-label use of injectable naloxone solution as nasal spray as a suitable alternative to licensed naloxone for injection (ACMD, 2012).

This chapter neither condemns nor condones the pragmatic provision of IN naloxone by public health initiatives, particularly in communities where the distribution of injectable naloxone is legally or politically not feasible. Rather, the scope of the chapter is to discuss the unlicensed use of new drug formulations in the addictions treatment field by raising the question whether the bypassing of product testing and efficacy be justified when licensed naloxone products already exist. The chapter has two aims:

- Aim 1: to assess the provision of improvised nasal naloxone in clinical practice
- Aim 2: to examine published evidence of pharmacokinetics and effectiveness of naloxone by nasal administration relative to injection.

4.2 Methods

4.2.1 Search strategy

A systematic search was conducted to document existing nasal naloxone distribution schemes and published evidence of pharmacokinetics. Replicating an earlier peer-reviewed search strategy reported by Kerr et al. in their review of intranasal naloxone for the treatment of suspected heroin overdose (Kerr, Dietze, & Kelly, 2008), the Cinahl, Cochrane, Embase and Medline databases were searched to identify relevant peer-reviewed English-language articles published between January 1946 and January (4th week) 2015 using the terms: ‘naloxone.mp’ or ‘exp naloxone’, ‘narcan.mp.’ or ‘exp.Narcan’ and ‘exp administration, intranasal/or intranasal.mp’ or ‘nose.mp’. I conducted the initial data searches, and the same process was replicated independently by a colleague (who was a co-author of the *Addiction* paper). I then screened papers for eligibility and extracted data under supervision of my first supervisor. 388 papers were retrieved and screened for original research (including case reports) reporting on pharmacokinetics, safety or effectiveness data of IN naloxone administration in healthy

volunteers or patients with suspected opioid overdose. Eighteen records matched our search criteria (Barton et al., 2005; Barton et al., 2002; Belz, Lieb, Rea, & Eisenberg, 2006; Doe-Simkins et al., 2009; Dowling et al., 2008; Green, Ray, Bowman, McKenzie, & Rich, 2014; Kelly et al., 2005; Kelly & Koutsogiannis, 2002; Kerr, Kelly, Dietze, Jolley, & Barger, 2009; Loimer, Hofmann, & Chaudhry, 1992; Loimer, Hofmann, & Chaudhry, 1994; Merlin et al., 2010; Robertson, Hendey, Stroh, & Shalit, 2009; Sabzghabaee, Eizadi-Mood, Yaraghi, & Zandifar, 2014; Walley, Doe-Simkins, et al., 2013; Walley, Xuan, et al., 2013; Weber, Tataris, Hoffman, Aks, & Mycyk, 2012; Zuckerman, Weisberg, & Boyer, 2014) (see Table 12 & Figure 15).

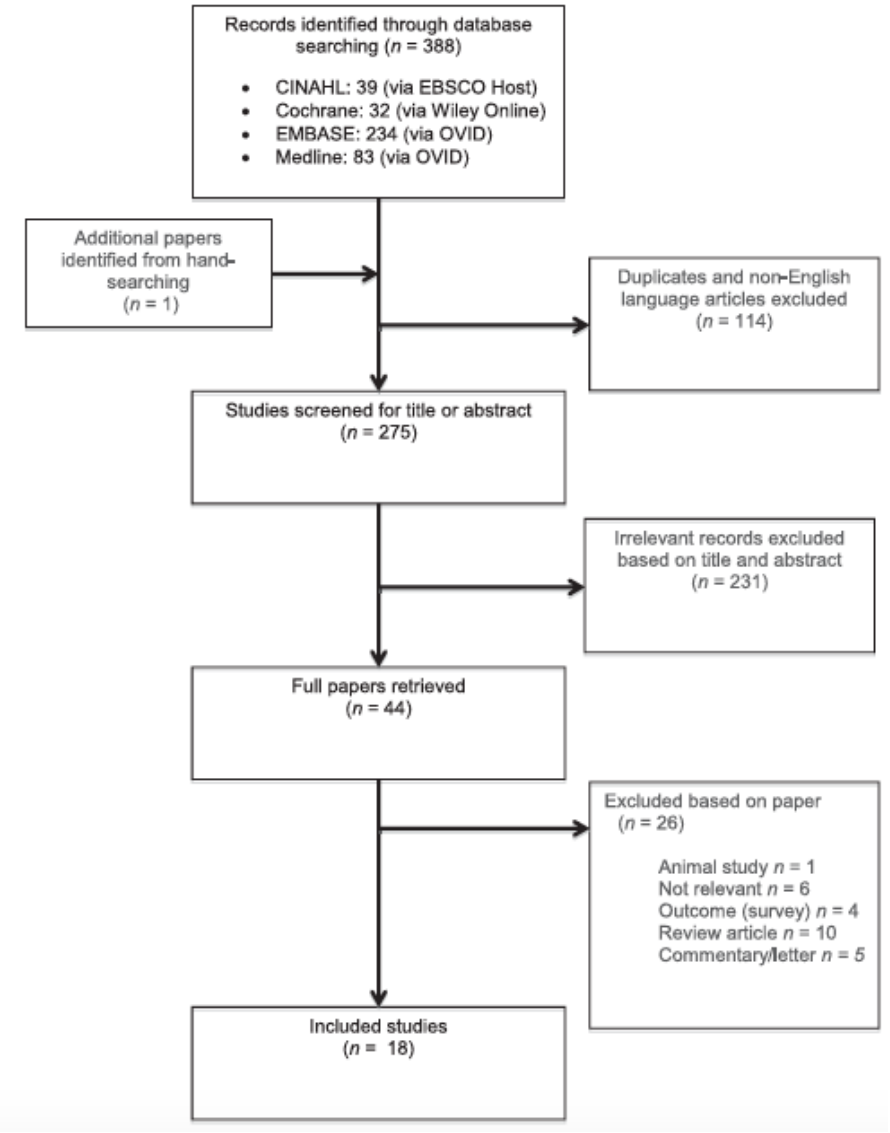

Figure 15 Flowchart of study selection

In addition, the World Health Organization International Clinical Trials Registry Platform (ICTRP) and the U.S. National Institutes of Health (NIH) Research Portfolio Online

Reporting Tools (RePORT) database were searched for ongoing studies investigating nasal naloxone. The ICTRP links national and regional clinical trials registers with the aim to facilitate registration of all international clinical trials and public accessibility of the trial information (WHO, 2017). The RePORT database captures all research activity funded by the US NIH.

4.3 Results

4.3.1 Current use of intranasal naloxone in clinical practice

Ambulance use

Nasal naloxone for treatment of opioid overdose was introduced as regular clinical practice (although without licensed approval for this route) into ambulance services in parts of the US (Denver, Colorado; Fresno, California; among others) in the 2000s (Barton et al., 2002; Belz et al., 2006; Robertson et al., 2009), and in several NHS Ambulance Service Trusts in the UK (incl. South Western, Great Western, and East Midlands).

Figure 16 Assembly of the Massachusetts take-home naloxone kit[16]

Take-home supply

Take-home naloxone as nasal spray only (i.e. without supplementary needle for IM injection) was first introduced in the US in Boston/Massachusetts in 2006 (Doe-Simkins et al., 2009). Assembly of the Massachusetts take-home naloxone kit for intranasal use

[16] Source: http://www.bu.edu/today/2013/addiction-research-alexander-walley/

is depicted in Figure 16. In 2013, over a third (i.e. 38%; 51 out of 136) of US organizations reported providing only improvised intranasal naloxone kits (CDC, 2015). In Europe, the Norwegian take-home naloxone scheme began providing only intranasal naloxone in 2014 (Clausen, 2014). At the time of writing, it was also proposed that the nasal spray would be the only form of naloxone provided in parts of Scotland (Inverness and surrounding regions Highland, Argyll and Buke) (Greig, 2012) and in France (EMCDDA, 2016a).

4.3.2 Evidence-base for non-concentrated intranasal naloxone

No systematic review exists on nasal naloxone to date, but there is growing evidence of IN administration of naloxone reversing opioid overdose: At least 327 overdose reversals using nasal naloxone kits were reported in the Massachusetts-based take-home naloxone program (4, 28, 29). In ambulance and hospital-based trials, the time from dose administration to clinical response often took longer for nasal administration compared to injectable routes (18, 24, 25). However, for the comparison of IN and IV routes, this time difference disappeared when measuring the time from patient contact to clinical response due to the time saved for having to establish IV access (24). Similarly, the time to clinical response was no different from IM administration when a less dilute nasal spray formulation (2mg/mL) was used (19).

However, for reasons summarized below, there remains a lack of information about how adequately and reliably non-concentrated naloxone is absorbed intranasally.

Lack of simple pharmacokinetics

Progress with basic pharmacokinetic study of intranasal naloxone has been slow. The only pharmacokinetic study (Dowling et al., 2008) published by the time of writing (January 2016) reported extremely poor bioavailability (4%) for nasal naloxone (2mg/5mL), although the authors acknowledged that the dilute solution probably resulted in post-nasal loss or nasal leakage. Despite reports of replication studies (e.g. by pharmaceutical companies), no pharmacokinetics data had yet been published at the time of writing.

Non-response rate: The results from ambulance-based studies in Australia (Kelly et al., 2005; Kerr et al., 2009) and the US (Barton et al., 2002; Belz et al., 2006; Robertson et al., 2009) indicate that not all opioid overdose victims respond to nasal naloxone, with some needing a rescue dose of IM or IV naloxone (see also Table 12). An ambulance-based randomized trial in Australia compared IN to IM naloxone: in many instances, the

intranasal dose (2mg/5mL) was sufficient. However, it was not equal - the IN group was twice as likely to require rescue naloxone (26% IN group versus 13% IM group; p = 0.056; odds ratio (OR) = 2.4; 95% confidence interval (CI) = 1.0–5.7) (Kelly et al., 2005). In a replication trial with a more concentrated nasal spray formulation (2mg/mL), 18% of the IN group still needed rescue naloxone, which was significantly higher than the IM group (5%) (Kerr et al., 2009). This rate is broadly consistent with 16% of IN non-responders in a Denver-based observational trial (Barton et al., 2005). Other studies have reported non-response rates between 9% and 23% (14, 23, 26).

4.3.3 Ongoing research

Clinical trials are currently being conducted in the ambulance setting in Cincinnati, US, and in a supervised injecting clinic in Sydney, Australia. Pharmacokinetic exploration of IN formulations is finally underway by at least three groups in the US and Norway: however, no results were published at the time of writing (January 2016). Other potential non-injectable routes warrant consideration, which are explored more fully in Chapter 5.

4.4 Discussion

The concerns raised in this chapter relate to the use of improvised nasal sprays based on dilute solutions of naloxone developed for injection and not examined for suitability or efficacy as nasal spray.

4.4.1 Statement of principal findings

While FDA-approval of a concentrated naloxone nasal spray (4mg/0.1mL) in the US (Dowling et al., 2008) in late 2015 (FDA, 2015) was a step change, the following reasons for caution regarding the use of improvised naloxone nasal sprays remain: Firstly, non-response rates of between 9% and 26% have been reported for non-concentrated nasal naloxone (12, 14, 18, 19, 23, 26). As noted in the Introduction section, there is an inherent safety in the use of dilute nasal naloxone in the ambulance or hospital context where a naloxone injection can be administered if the initial nasal naloxone does not reverse overdose. However, in take-home naloxone schemes that *only* provide naloxone for off-label IN use (Doe-Simkins et al., 2009; Madah-Amiri et al., 2017), the absence of a back-up injection is a crucial difference. In this situation, the failure of effect of IN naloxone, for whatever reason, can delay the time to naloxone injection until an ambulance arrives. In the emergency management of opioid-induced respiratory depression, time is of essence. Secondly, there is uncertainty about dose adequacy and

comparability of nasal naloxone. For the improvised nasal spray, the only commercially available injectable formulations have concentrations from 0.4mg/mL to 1mg/mL (adult formulations). Drug administration via nasal spray typically involves giving 0.1mL per nostril, with 0.25mL considered the maximum, as any greater volume is likely lost post-nasally (and then swallowed and consequently inactivated) or by nasal drip (and thereby lost) (Dowling et al., 2008).

4.4.2 Possible mechanisms and implications for clinicians

Some consideration of the practical administration of the naloxone as nasal spray is warranted. The most concentrated injectable formulation of naloxone available is 2mg/2mL. If this concentration of naloxone is administered at 0.25mL per nostril, then, even if one discounts the reported nasal bioavailability of 4% (Dowling et al., 2008) and optimistically assumes that 40% of naloxone is absorbed, the effective IN dose would be only 0.2mg, i.e. equivalent to only half the lower recommended injectable dose. The remainder would be lost as nasal drip or as post-nasal drip (and inactivation as part of first-pass metabolism).

Given the small dose that is probably absorbed, reported benefit from improvised nasal naloxone devices (see Table 12) is puzzling: this should prompt challenge to assumptions about naloxone dose-response. Dose-ranging studies with dependent volunteers might explore this sensitively (see Chapter 10).

Thirdly, at a practical level, uncertainties about the effectiveness of a nasal spray include: the need for a spray device to function in horizontal position, the impact of compromised nasal mucosa (e.g. chronic ulceration from drug snorting (Peyrière et al., 2013), and the risk of obstruction from opioid-induced vomit. Any factors which reduce or delay the nasal absorption of naloxone may lessen the overdose victim's chance of survival.

Finally, some consideration needs to be given to why a clinician would prescribe naloxone for use by an unlicensed route, when a highly effective, licensed injection is already in their armamentarium. Perhaps the nasal spray relieves layperson anxiety about giving an IM injection. However, families of patients with other disorders successfully overcome this fear (e.g., EpiPen, glucagon). Training in technique is necessary, but this can be done efficiently and bolsters the confidence of family and peers to intervene (Williams et al., 2014).

4.4.3 Possible mechanisms and implications for policymakers

In jurisdictions where laypeople (including family members) are prohibited from administering emergency medications by injection, there should be urgent challenge of this policy. It cannot be ruled out that medico-professional and medico-legal risks may arise when naloxone is prescribed for use by unlicensed route, especially when licensed naloxone products are applicable. If death were to occur following nasal administration, what reason would justify having provided naloxone for use by an unlicensed route? It follows that, wherever possible, clinicians should prescribe medications for use by the approved routes of proven effectiveness.

For any novel non-injectable naloxone products, the cost needs to be considered. The pricing of nasal naloxone products that are currently under development or under review is uncertain. Affordability relative to existing injectable products will be crucial, particularly for the proposed population-wide provision of emergency naloxone, as articulated by the World Health Organization (WHO, 2014).

4.4.4 Questions for future research

What data should be available on nasal naloxone formulations?

Any novel non-injectable naloxone formulation would need to be absorbed to a sufficient extent so as to produce the life-saving reversal of opioid effect (for which emergency reason it is being given).

Pharmacokinetics and study of bioavailability need to be undertaken in healthy volunteers and published showing acceptable bioavailability and reliability across subjects before incorporation into standard clinical practice.

Human volunteer data may also need to be supplemented with clinical safety data. It is not obvious that nasal administration would be equivalent in healthy volunteers and opioid overdose victims. The overdose victim's past drug use may have caused damage to the mucosa and structure of the nose, and the overdose crisis may have resulted in vomitus or secretions in the nasal cavity. These challenges need to be examined and addressed.

What are the potential specifications for an acceptable naloxone nasal spray?

From the above analysis of the insufficiencies of improvised naloxone nasal spray, it is possible to deduct some of the key features of an acceptable nasal naloxone formulation.

Firstly, in view of the emergency context of the resuscitation and the likely unconscious state of the overdose victim, the nasal device would need to be functional in all orientations (i.e. not just when held vertically, as with many nasal sprays).

Secondly, putting to one side the Dowling et al. finding of 4% bioavailability (2008), if one assumes a more optimistic 40% bioavailability for nasal naloxone as well as an absorption volume of up to 0.25mL of fluid per nostril, then a more concentrated solution is required – perhaps between 4mg/ml up to 20mg/ml. Fortunately, naloxone is highly soluble (Rang et al., 2012) (see Chapter 1), so this should not be a problem, provided there are no adverse local effects.

Thirdly, it needs to be established that the speed of onset is sufficient. In addition to adequate overall absorption, it is essential that the absorption occurs rapidly, given the emergency of the overdose. A rapid onset of action with detectable effect within 5 minutes and good effect within 10 minutes will likely be needed. Measures of T_{max} (i.e. the time at which the maximum blood serum concentration of naloxone is observed) may not capture the shape of onset of effect. The time taken to achieve blood levels of 50% of those subsequently recorded as C_{max} (hereafter referred to as $T_{50\%}$) may constitute an alternative pharmacokinetic parameter worth exploring.

4.5 Conclusion

There are good reasons to want a non-injectable naloxone preparation for treating opioid overdose to work. However, wishing for a product is not the same as demonstrating efficacy and effectiveness. The benchmark for any non-injectable naloxone product, if considered for wider community use, should be that it is, in general terms at least, as effective and reliable as the licensed injection.

Description of use of improvised nasal formulations should not be accepted as evidence of effectiveness. Actual data need to be published and need to report not only on whether it is effective in some subjects, but also whether it is effective in all subjects. If no licensed injectable comparator existed, then a new overdose resuscitation medication that was effective for many subjects would be valued, even if it was not effective for all subjects. However, as established, licensed injectable naloxone with proven efficacy and good safety profile already exists, the expectations for potential new naloxone formulations are at a higher bar.

To conclude, outside clinical trial contexts, clinicians should prescribe take-home naloxone only as one of its licensed formulations, since it remains uncertain how adequately and reliably the improvised nasal spray is absorbed. Or, if clinicians choose to prescribe the improvised naloxone nasal spray off-license, then they should include a

needle in the naloxone kit to allow for a back-up injection if the nasal spray is insufficient. Evidence of adequate bioavailability and acceptable pharmacokinetic curves are vital preliminary steps for non-injectable naloxone formulations, especially when effective approved injectable formulations exist. And yet, the clinical and scientific communities have failed to ask these basic questions around the use of improvised nasal kits. The evidence base for the efficacy of improvised kits is insufficient and highlights the need for the development of purpose-made non-injectable naloxone formulations. Chapter 5 explores candidate routes for non-injectable naloxone administration.

Table 12 Summary of included studies

Author (year)	Study design	Setting	N	IN Dose	Dose comparator	Outcomes of naloxone administration
Barton et al. (2002)	Case series	Pre-hospital (EMS)	30 patients	2mg (as 1mg/ml)	2mg IV if no immediate response	11 patients responded to naloxone challenge (IN or IV), of which 10 (91%) responded to IN alone, with an average response time of 3.4 minutes.
Barton et al. (2005)	Case series	Pre-hospital (EMS)	95 patients	2mg (as 1mg/ml)	2mg IV if no immediate response	52 patients responded to naloxone challenge (IN or IV), of which 43 (83%) responded to IN alone, with an average response time of 4.2 minutes.
Belz et al. (2006)	Case series	Pre-hospital (EMS)	164 patients (108 IV; 29 IV+IM; 18 IM; 2 IN; 1 IM+IN; 6 NR)	Median 1mg (0.2mg-2mg) across all routes of administration	IV, IM, IV+IM, IM+IN (doses NR)	119 (73%) patients fully or partially responded to naloxone (for all routes of administration). 36 (22%) cases of death, 25 (15%) cases of agitation, 6 cases (4%) of emesis.
Doe-Simkins et al. (2009)	Pre-post comparison	Take-home naloxone	385 opioid users	2mg (2mg/2ml)	None	Participants reported 74 successful OD reversals; no deaths.
Dowling et al. (2008)	Crossover (open label)	Laboratory (pharmacokinetics)	6 healthy volunteers	0.8mg, 2mg (as 0.4mg/ml)	0.8mg IM, 0.8mg IV, 2mg IV	The bioavailability was 36% for IM and 4% for IN, both relative to IV.
Green et al. (2014)	Case report	Take-home naloxone	2 opioid users	2mg (2mg/2ml)	None	Participants reported 2 successful OD reversals (self-administration); no deaths.
Kelly et al. (2005)	Randomized trial	Pre-hospital (EMS)	155 patients (71 IM, 84 IN)	2mg/5ml	2mg IM	The IM group had more rapid respiratory response than IN group (significant group difference in 'time to RR > 10/min' and 'spontaneous respiration within 8 min'). No group difference in GCS scores or need for rescue naloxone (13% IM v 26% IN).
Kelly & Koutsogiannis (2002)	Case report	Hospital (ED)	6 patients	0.8mg-2mg	None	Across all patients, return of adequate spontaneous respiration occurred within a median 50 seconds (min. 30 seconds, max. 2 minutes).
Kerr et al. (2009)	Randomized trial	Pre-hospital (EMS)	172 patients (89 IM, 83 IN)	2mg (2mg/ml)	2mg IM	The rates of response within 10 minutes were similar: IN naloxone (60/83, 72.3%) compared with IM naloxone (69/89, 77.5%). No group difference in

Author (year)	Study design	Setting	N	IN Dose	Dose comparator	Outcomes of naloxone administration
						mean response time (IN: 8.0, IM: 7.9 minutes). Significant group difference in need for rescue naloxone: IN 18% vs. IM 5%.
Loimer et al. (1992)	Controlled prospective trial (non-randomized)	Hospital (jail-based)	30 (22 opiate-dependent, 8 control)	1mg (1mg/0.4ml)	None	After opioid challenge test of IN naloxone administration, opiate-dependent patients showed significantly higher ratings on withdrawal scale for up to 30 minutes (in comparison to controls).
Loimer et al. (1994)	Randomized trial	Hospital	17 patients (7 IV vs. IM; 10 IV vs. IN)	1mg (1mg/0.4ml)	1mg IM (1mg IV as pre-treatment in both groups)	Both IN and IM groups showed significant withdrawal symptoms at 15 and 45 minutes. Only the IN group had significant withdrawal symptoms at 5 minutes, suggesting that onset of IN naloxone is faster than IM.
Merlin et al. (2010)	Retrospective chart review	Pre-hospital (EMS)	93 (38 IN, 55 IV) (analysis of subsample of total 344 cases)	2mg (1mg per nostril)	IV naloxone titrated to effect (average 2mg)	No group difference in RR or GCS pre-naloxone administration. Post naloxone administration, both the median RR and GCS scores were significantly higher for the IV group than the IN group. 9 IN patients (23%) required rescue IV naloxone.
Robertson et al. (2009)	Retrospective chart review	Pre-hospital (EMS) and hospital (ED)	154 patients (50 IN, 104 IV)	2mg (1mg per nostril)	1mg IV	The time from dose administration to clinical response (pre-defined change in RR and GCS of 6 points) took significantly longer for IN route (12.9 vs. 8.1 min). No group difference in overall time from patient contact to response. More IN patients received 2 doses of naloxone (34% vs. 18%, p = 0.05), and 3 IN patients needed a rescue dose of IV or IM naloxone.
Sabzghabaee et al. (2014)	Randomized trial	Hospital (ED)	100 patients (50 IN, 50 IV)	0.4mg (0.4mg/2ml, i.e. 1ml per nostril)	0.4mg IV	Response to naloxone was significantly slower in IN group. Patients in IN naloxone had higher GCS scores but lower heart rate than IV group. No group

Author (year)	Study design	Setting	N	IN Dose	Dose comparator	Outcomes of naloxone administration
						difference in blood pressure, RR, arterial O2 saturation, or length of hospital stay.
Walley, Xuan, et al. (2013)	Interrupted time-series analysis	Take-home naloxone	2,912 opioid users	2mg (2mg/2ml)	Communities without take-home naloxone	Participants reported 327 successful OD reversals; no deaths. OD mortality rates were reduced in communities with THN, compared to those without.
Walley, Doe-Simkins, et al. (2013)	Pre-post comparison	Take-home naloxone	1,553 methadone clients	2mg (2mg/2ml)	None	Methadone clients reported 92 successful OD reversals; no deaths.
Weber et al. (2012)	Retrospective chart review	Pre-hospital (EMS)	105 patients	2mg (2mg/3ml)	None	Of all 105 cases, 23 (22%) had complete response, 62 (59%) partial response, and 20 (19%) no response, as indicated by GCS score and RR. Eleven cases (10%) received rescue naloxone (6 IV, 5 IM). No adverse events or deaths occurred.
Zuckerman et al. (2014)	Case report	Pre-hospital (EMS) and hospital (ED)	1 patient	2mg (1mg per nostril)	None;	After non-response to IN dose, patient was administered 3 IV rescue doses (1mg + 0.4mg + 0.4mg) by EMS and ED staff.

Annotations: ED - emergency department; EMS - emergency medical services; GCS – Glasgow Coma Scale; IM - intramuscular, IN – intranasal; IV – intravenous; NR - not reported; RR - respiration rate

Chapter 5 Non-injectable Routes of Naloxone Administration

Preface

In response to rising overdose mortality rates, the US FDA, Centers for Disease Control and Prevention (CDC), National Institute on Drug Abuse (NIDA), and Office of the Assistant Secretary for Health and Human Services (HHS) sponsored a stakeholder meeting on April 12, 2012 to "discuss whether naloxone should be made more widely available to trained laypersons in an effort to reduce deaths due to opioid overdose" (FDA, 2012).

The meeting set the scene for novel naloxone products for layperson use. The FDA strongly encouraged the development of non-injectable naloxone products and presented key regulatory criteria that would apply to any New Drug Application (NDA) for naloxone (Hertz, 2012; Nadel, 2016). NIDA subsequently announced that it would provide funding for the development of "user friendly delivery systems for naloxone (i.e., intranasal rather than injection)" (Volkow et al., 2014).

To address the need for non-injectable naloxone for layperson use, I conducted a systematic review between July 2015 and January 2016, which applied the FDA criteria to possible routes of administration to evaluate their suitability for the community-based management of opioid overdose. Three candidate routes for injection-free naloxone administration were identified: buccal, nasal, and sublingual. My analysis forms the basis of this chapter and has been published as co-first-authored paper "Naloxone without the needle – systematic review of candidate routes for non-injectable naloxone for opioid overdose reversal" in *Drug and Alcohol Dependence* (Strang, McDonald, Alqurshi, et al., 2016). The publication was developed in co-authorship with my first and second supervisor as well as with colleagues Dr. Abdulmalik Alqurshi, Dr. Paul Royall, and Professor Ben Forbes from the Institute at Pharmaceutical Science at King's College London.

In this chapter, I integrate evidence from the peer-reviewed literature. I capture research and development activity within pharmaceutical industry in Chapter 6 where I provide a synthesis of evidence from international patent applications.

5.1 Introduction

Naloxone without needles would have many advantages over existing injectable products. Firstly, injectable medications are intimidating for laypersons to use (Beletsky, Rich, & Walley, 2012) and present logistical barriers: they require product assembly (e.g. needle and syringe) and training in administration. Secondly, with use of naloxone by injection, there is the risk of needle-stick injury and contraction of blood-borne diseases (e.g. hepatitis C, HIV), which are highly prevalent among people who inject drugs (Degenhardt et al., 2016). Thirdly, non-injectable naloxone could likely overcome regulatory obstacles (e.g. prescription-only status for injectable medications) and be more easily provided to a wider intervention workforce (e.g. hostel staff, outreach workers, police, etc.).

New methods of delivery for naloxone need to be suitable for layperson use in community-based settings. Furthermore, formulations should be developed with longer shelf-life, especially in view of the pre-provision of these naloxone products to community and families and other non-hospital settings. Naloxone also needs to be absorbed rapidly, given the emergency situation, in quantity sufficient to effect quick reversal of opioid-induced respiratory depression.

The reference for any candidate non-injectable routes is injectable naloxone, administered by the licensed intramuscular (IM), intravenous (IV), and subcutaneous (S/C) routes (WHO, 2014). When administered by the IM or S/C routes, naloxone typically reverses opioid action within 3-7 minutes; whereas the effect from IV administration has an onset typically within 2 minutes (UNODC/WHO, 2013). With long-standing approval for, and experience with, naloxone in injectable form, this sets the standard against which possible non-injectable formulations need to be measured (Hertz, 2012).

This chapter examines the options for non-injectable naloxone with potential application for wider community-based opioid overdose reversal. The aims are twofold:

- Aim 1: to identify candidate routes of injection-free naloxone administration potentially suitable for emergency overdose reversal;
- Aim 2: to consider pathways for developing and evaluating novel naloxone formulations.

Table 13 Second stage of selection process: Search protocol

Research question	**What are the results of in vivo naloxone administration by the buccal, nasal, and sublingual routes of administration?** Aim: To assess the feasibility of non-injectable naloxone administration
Search strategy	**Electronic Databases:** PubMed to identify relevant peer-reviewed articles published in English language between January 1946 and January (4th week) 2016. *Buccal naloxone – search details:* ("naloxone"[MeSH Terms] OR "naloxone"[All Fields]) AND buccal[All Fields] *Nasal naloxone – search details:* ("naloxone"[MeSH Terms] OR "naloxone"[All Fields]) AND (("nose"[MeSH Terms] OR "nose"[All Fields]) OR ("nose"[MeSH Terms] OR "nose"[All Fields] OR "nasal"[All Fields]) OR intranasal[All Fields]) *Sublingual naloxone – search details:* ("naloxone"[MeSH Terms] OR "naloxone"[All Fields]) AND ("administration, sublingual"[MeSH Terms] OR ("administration"[All Fields] AND "sublingual"[All Fields]) OR "sublingual administration"[All Fields] OR "sublingual"[All Fields]) **Hand-search:** The reference lists of relevant studies identified via PubMed were manually searched for additional studies meeting the below eligibility criteria.
General search filter used	Identify records from title, abstract, keywords; Map term to Medical Subject Heading Publication Year: 1946 – Current Duplicate articles to be removed using EndNote software version X6 for Windows.
Search Date	1 January 1946 to January (4th week) 2016
Eligibility criteria	
• Population	Non-human animals OR humans (healthy volunteers OR opioid users)
• Intervention	Naloxone administration (in vivo)
• Comparison	Parenteral naloxone administration (if available)
• Outcomes	Pharmacokinetics data Pharmacodynamics data Overdose outcomes (death vs. successful reversal) Adverse reactions
• Study design	Pre-clinical and clinical studies (randomized or observational trials)
• Publication status	Original studies published in peer-reviewed journals
Exclusion criteria	Case reports Qualitative studies Reporting on naloxone / buprenorphine Not reporting on naloxone Not reporting primary research data
Analysis method	Narrative synthesis

5.2 Methods

A three-stage approach has been taken (see Figure 17). The first stage was an examination of all 112 routes of drug administration listed by the FDA (FDA, 1992)-updated 2014). For each of the 112 possible routes of administration, the potential applicability as a viable non-injectable route for emergency naloxone delivery by non-medical personnel was considered (see Table 16).

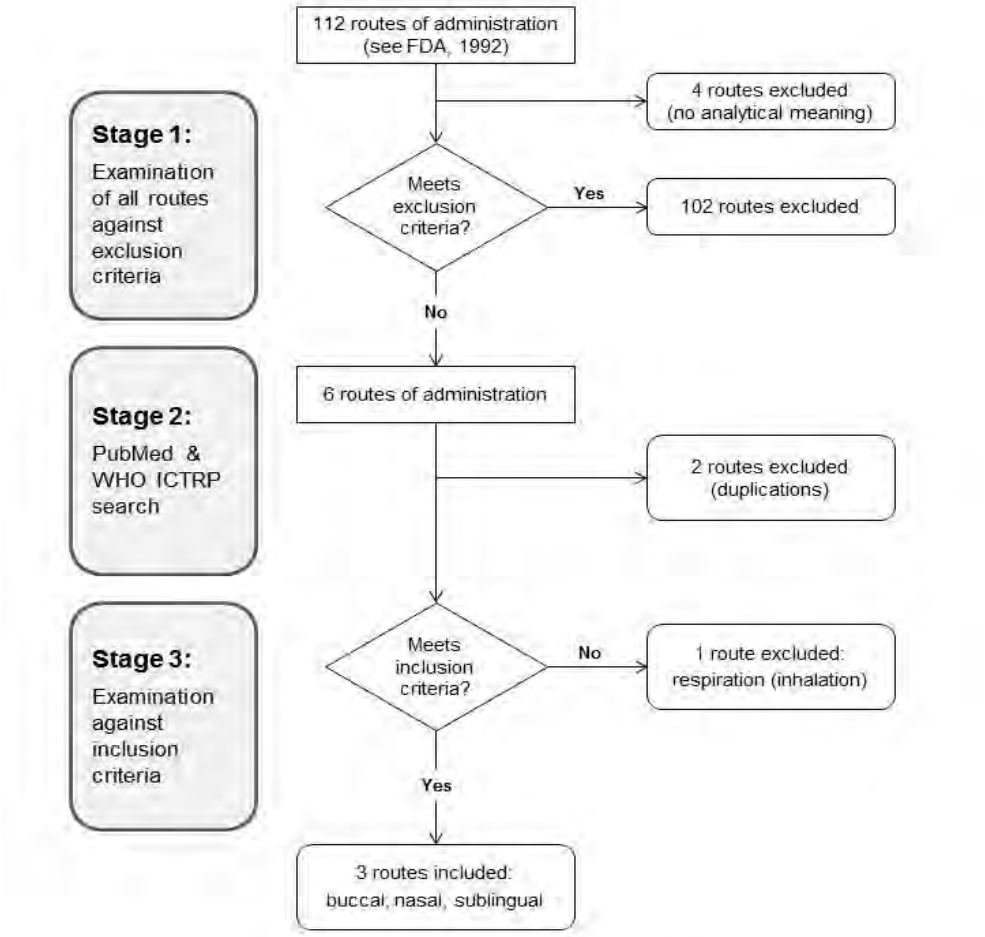

Figure 17 Selection process of candidate routes of administration

Routes of administration were thus identified as unsuitable according to five exclusion criteria:

i) if the drug administration is by injection (or similar invasive procedure);

ii) if the route is only relevant to medical procedures or requires medical training;

iii) if the route is not publicly acceptable for administration by non-medical bystanders (e.g. rectal or vaginal administration);

iv) if the route does not produce adequate systemic drug concentrations;

v) if the route does not produce sufficiently rapid drug absorption relative to parenteral administration (Hertz, 2012).

The second stage was to systematically search PubMed and the WHO International Clinical Trials Registry Platform for the potential candidate routes of administration that had emerged from the first stage. The search term "naloxone AND [route of administration]" (e.g. "naloxone AND (nose OR nasal OR intranasal)") was used for each route across the electronic databases (see Table 13 for search protocol). I conducted the search and assessed retrieved studies for eligibility under supervision of my first supervisor. Relevant original research studies that were published in English language and reported on the outcomes of in vivo naloxone administration (e.g. overdose reversals, pharmacokinetics/-dynamics data) in humans or animals were included in this analysis (see Figure 18 for PRISMA diagram). A list of the eleven ineligible studies that were excluded after full-text review is provided in Table 14.

The third stage, for remaining potential non-injectable routes of administration, comprised a more rigorous examination of the evidence against the inclusion criteria (see also Table 15):

i) the route is suitable for overdose emergency situation;
ii) the route does not bear major risk of compromise from overdose complication.

For the first and third stage, I used the specified exclusion and inclusion criteria to screen all relevant routes of administration for potential inclusion, and the same process was conducted independently by my first supervisor. In cases of disagreement, a third colleague (who was a co-author of the *Drug and Alcohol Dependence* paper) acted as the final arbitrator for inclusion or exclusion of a route.

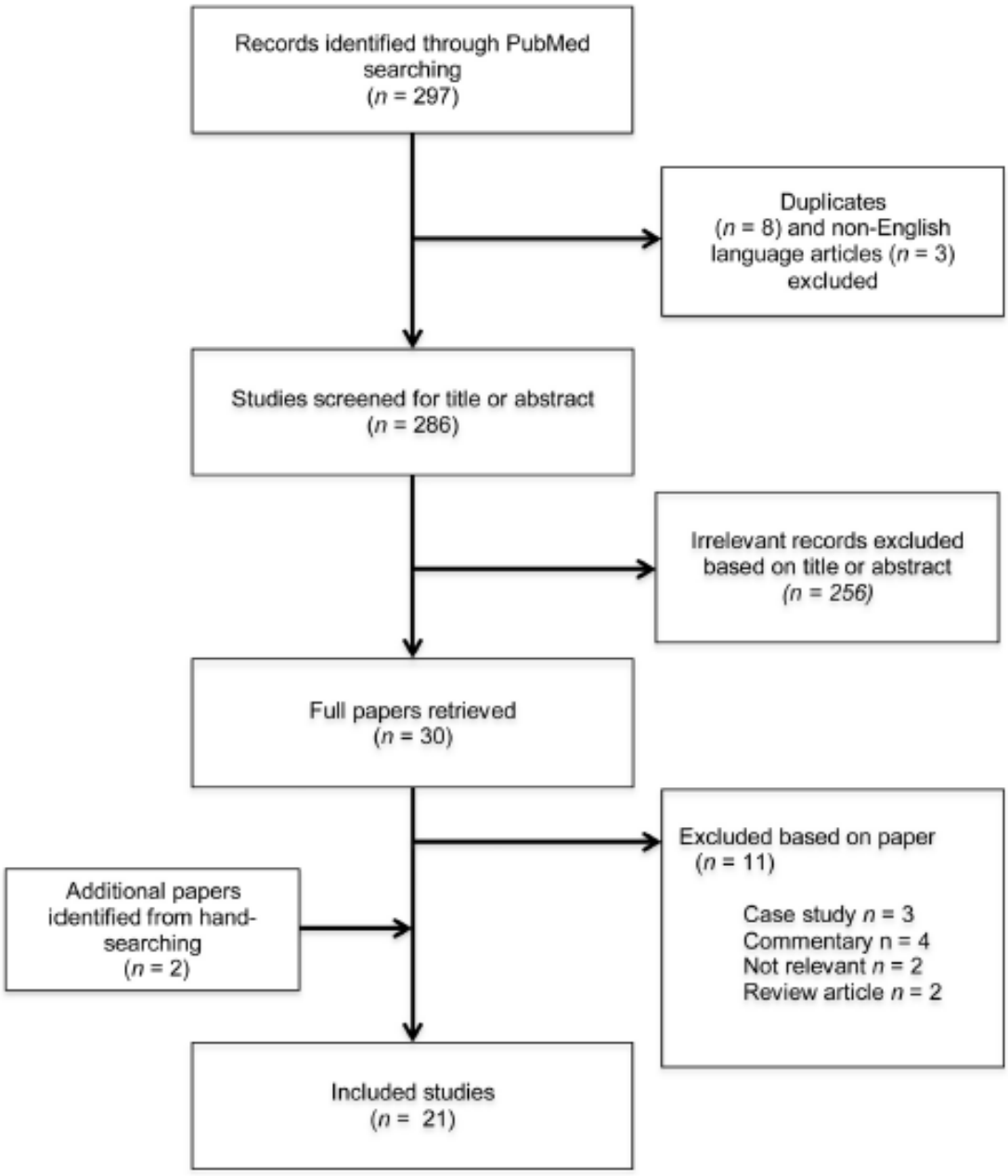

Figure 18 PRISMA diagram of study selection

5.3 Results

5.3.1 Shortlisting potential non-injectable routes of administration

From examination of all 112 listed routes of administration (FDA, 1992), four were excluded on the basis that they held no analytic relevance ('unassigned', 'unknown', 'other' and 'not applicable'). From the remaining 108 categories, a further 102 were excluded according to the criteria listed in 'Method' (see Table 16). For instance, enteral delivery (through the gastro-intestinal mucosa) was excluded because of insufficient systemic absorption, since naloxone is poorly bioavailable if swallowed due to high first-pass metabolism (Fishman et al., 1973). After this process, six non-injectable candidate routes remained to be considered further (see Table 15). Two of these six routes (see in italics at bottom of Table 15) were then removed on the basis that they were overarching categories of routes already being considered. Thus 'oropharyngeal' was removed as substantially overlapping with 'buccal' and 'sublingual', and 'transmucosal' was removed and considered under the specific mucosa ('buccal', 'intranasal', 'sublingual'). With regard to the wider range of possible transmucosal routes, rectal delivery, which has replaced administration by injection for several emergency medications in pediatric care (Lyon & McIntosh, 1985; NICE, 2009), was specifically not included for further consideration, since it is unlikely to be acceptable to family and peers for community-based naloxone emergency administration to overdose victims.

Table 14 Studies excluded after full-text review (n=11)

Study ID	DOI / URL	Search Source	Reason for exclusion
Davis (2015)	10.3109/10903127.2014.942484	PubMed	Commentary
Fareed (2015)	10.1111/ajad.12230	PubMed	Case report
Green (2014)	10.1080/08897077.2013.825691	PubMed	Case report
Kelly (2002)	10.1136/emj.19.4.375	PubMed	Commentary
Kerr (2008)	10.1111/j.1360-0443.2007.02097.x	PubMed	Review article
Klimas (2015)	10.1186/s12909-015-0487-y	PubMed	Not relevant
Lenton (2015)	10.1111/dar.12198	PubMed	Not relevant
Traynor (2016)	10.2146/news160002	PubMed	Commentary
Wermeling (2010)	10.1592/phco.30.7.627	PubMed	Commentary
Wolfe (2004)	10.1016/j.jen.2004.01.006	PubMed	Review article
Zuckerman (2014)	10.3109/10903127.2014.896961	PubMed	Case report

5.3.2 Fuller examination of the shortlisted potential non-injectable routes

As next step, these four potential routes (buccal, nasal, sublingual, respiratory/inhalation) were examined more fully based on the literature retrieved from the electronic databases. According to the WHO International Clinical Trials Registry Platform, nasal naloxone was being investigated in clinical trials by the Norwegian University of Science and Technology (NCT02307721, NCT01939444), in the US by the University of Cincinnati (NCT01912573) and Lightlake Sinclair Ltd. (NCT01567670), in Jordan by Mitovie Pharma Ltd (NCT01622504), and in Australia at the Sydney Medically Supervised Injecting Centre (ACTRN12611000852954). No database entries were found for study of naloxone via the buccal, sublingual or respiratory/inhalation routes. Each of these four routes of administration was then considered in turn:

Respiratory (inhalation)

The 'Respiratory (Inhalation)' route was excluded as not being suitable for further consideration because the victim might no longer be breathing (or breathing only very shallowly). Further, current portable devices for drug delivery to the lungs could not be used reliably in an emergency situation by non-medical personnel (spray or aerosolized naloxone is better considered under the ‘nasal’ category).

Sublingual

For the sublingual route, I identified one pharmacodynamics study in opioid-dependent volunteers (via PubMed), where sublingual naloxone precipitated withdrawal symptoms in 5 out of 9 participants (Preston, Bigelow, & Liebson, 1990). Apart from separate work on buprenorphine/naloxone combination, no further investigative work for sublingual was identified.

Nasal

PubMed search yielded 18 studies reporting in vivo administration of intranasal naloxone. Preclinical data from rodent studies showed complete absorption of nasal naloxone (bioavailability relative to IV: F% = 101%) (Hussain, Kimura, Chong-Heng, & Kashihara, 1984). In first in-human trials, nasal naloxone was found to elicit withdrawal symptoms in opioid-dependent volunteers (Loimer et al., 1992; Loimer et al., 1994).

Since the early 2000s, nasal naloxone has been used off-label by ambulance personnel (Barton et al., 2005; Barton et al., 2002; Belz et al., 2006; Kelly et al., 2005; Kerr et al., 2009; Merlin et al., 2010; Robertson, Hendey, Stroh, & Shalit, 2009; Weber, Tataris, Hoffman, Aks, & Mycyk, 2012) and in the emergency department (Sabzghabaee, Eizadi-Mood, Yaraghi, & Zandifar, 2014). More recently, improvised nasal kits (consisting of a pre-filled naloxone syringe and an atomizer which fits onto the syringe to generate a nasal spray) have been provided to opioid users, peers, and families in take-home naloxone trials (Doe-Simkins et al., 2009; Dwyer et al., 2015; Walley, Doe-Simkins, et al., 2013; Walley, Xuan, et al., 2013), and successful overdose reversals using improvised nasal kits have also been reported for police first responders (Rando et al., 2015). However, the only published pharmacokinetic study in humans found intranasal naloxone (2mg/5ml) had a relative bioavailability of only 4% (Dowling et al., 2008).

Buccal

PubMed search identified two preclinical studies on buccal naloxone. In rodents, buccal naloxone administration led to high bioavailability (F% = 69-71%) and a T_{max} (i.e. time from dosing to peak concentration) of 24 minutes (Hussain, Aungst, Kearney, & Shefter, 1987; Hussain, Aungst, Koval, & Shefter, 1988), whereas in dogs, despite buccal T_{max} at 18 minutes, bioavailability was low (16%) (Hussain et al., 1988).

Consequently, only three routes of administration were carried forward for full consideration as candidate routes of administration for emergency naloxone by non-medical personnel: nasal, sublingual and buccal. All three routes were then compared more fully against the FDA-identified reference route (injectable naloxone) (Hertz, 2012).

Table 15 Third stage of selection: inclusion criteria

			Inclusion criteria	
NAME	**DEFINITION**	**FDA CODE**	**Suitable for overdose crisis situation**	**No risk of compromise from overdose complication**
BUCCAL	Administration directed toward the cheek, generally from within the mouth.	030	**X**	**X**
NASAL	Administration to the nose; administered by way of the nose.	014	**X**	possible impairment due to O/D vomit or secretions
SUBLINGUAL	Administration beneath the tongue.	024	**X**	possible impairment due to O/D vomit or secretions or due to closed mouth
RESPIRATORY (INHALATION)	Administration within the respiratory tract by inhaling orally or nasally for local or systemic effect.	136	not viable as O/D victim not breathing or only shallowly	**X**
With the following routes subsumed into the above four routes:				
OROPHARYNGEAL	*Administration directly to the mouth and pharynx.*	*410*	*absorption likely too slow*	*possible impairment due to O/D vomit or secretions*
TRANSMUCOSAL	*Administration across the mucosa.*	*122*		*- as for buccal -*

5.3.3 Testing requirements: The 2012 FDA criteria

According to the FDA guidance (Hertz, 2012), pharmacokinetic studies would need to "[e]valuate the relative bioavailability of at least two different doses compared to parenteral injection of naloxone (IM, IV or SC). […]. [Studies should] [c]ompare a parenteral dose of naloxone of at least 0.4mg to dose(s) of the new product that would be expected to result in similar or greater drug exposure."

The regulatory benchmark is thus that a 0.4mg injectable dose (IM, IV, or SC) and one or multiple doses of the new non-injectable naloxone formulation need to result in comparable plasma naloxone levels (i.e. area under the curve; AUC).

The selection of the dose(s) of the new non-injectable product should be based on assumptions of its bioavailability, i.e. either based on previous data of naloxone bioavailability by the same route of administration, or if unavailable, the bioavailability of similar active ingredients by the same route of administration, or – if no human pharmacokinetic data is available – bioavailability of naloxone by the same route of administration in non-human animals.

Further, "[t]arget plasma naloxone levels [should be] detectable in all subjects for a meaningful duration comparable to approved product." In the emergency situation of opioid overdose, naloxone needs to be absorbed rapidly. Absorption would thus need to be at least as rapid as intramuscular injection, whereby onset of effect starts within 3 to 7 minutes of administration (WHO, 2014). Early naloxone exposure can be quantified by means of Tmax and partial areas under the curve (e.g. between dosing and Tmax). In addition, the FDA guidance (Hertz, 2012) outlines the following key questions concerning bioavailability and usability:

1) If the bioavailability of the new product compared with the approved intramuscular injection is low, then it is unclear if adequate efficacy can be reached. Vice versa, if the bioavailability of the new product is unexpectedly high, then this may have implications for the safety profile of the novel formulation.

2) "Can the product be used by the intended population, i.e. [is] administration by someone other than the patient [possible]?"

For all three identified candidate non-injectable routes (nasal, sublingual and buccal), investigators and manufacturers need to consider the FDA guidance on development of novel naloxone formulations for outpatient use (Hertz, 2012). The FDA proposed this strategy mindful of the good safety profile of naloxone: while naloxone blocks opiate

receptors, it has no pharmacological effect in individuals who are not opiate-dependent and do not have any opioids in their system. Moreover, as it has no potential of abuse due to lack of euphoriant effect (Brunton et al., 2010), the pharmacokinetics of novel naloxone formulations can thus be safely tested in healthy volunteers.

For all potential non-injectable naloxone products for use in overdose emergency management, naloxone will need to be absorbed rapidly into the bloodstream and thence across the blood-brain barrier. This is plausible for the nasal, buccal and sublingual routes, since they all involve absorption across a mucous membrane outside the gastro-intestinal tract. They drain to the peripheral circulation rather than the hepatic portal vein, thus avoiding the hepatic portal system and first-pass metabolism in the liver. In addition to these anatomical and pharmacological factors, the context of emergency overdose reversal needs to be considered. For instance, devices need to be portable, accessible, easy to use and also operational on an unconscious supine overdose victim). The impact of potential pre-existing physical health impairments in the target population, such as damage to, or obstruction of, the relevant mucosa also needs to be considered.

5.3.4 Intranasal naloxone

The nasal route is characterized by high blood perfusion of the nasal mucosa which facilitates transmucosal absorption, and drainage mainly occurs into the facial veins (Dale et al., 2006; Standring, 2015). An additional nose-to-brain (N2B) connection has been hypothesized. It is mooted that drugs could be transported directly into the cerebrospinal fluid via the olfactory and trigeminal nerves (Djupesland, Messina, & Mahmoud, 2014) through the olfactory epithelium (on the roof of the nasal cavity) projecting directly into the olfactory bulb. However, human evidence of direct drug transport from the nose to the cerebrospinal fluid is currently still lacking (Djupesland et al., 2014; Merkus, Guchelaar, Bosch, & Merkus, 2003)

Clinical reports describe use of improvised nasal naloxone kits which indicate life-saving benefit in many situations. However, for non-concentrate nasal kits, there remains uncertainty with regard to the formulation's bioavailability and reliability of clinical effectiveness (Strang, McDonald, Tas, & Day, 2016). For example, Dowling et al. (2008) found that non-concentrate nasal naloxone spray (2mg/5mL) had a bioavailability of only 4%, although the authors themselves acknowledged that the poor absorption was likely due to the insufficiently concentrated formulation. In two ambulance-based clinical trials, intranasal naloxone had a substantial non-response rate: among opioid overdose

victims, 26% (using 2mg/5mL nasal formulation) (Kelly et al., 2005) and 18% (using 2mg/mL nasal formulation) (Kerr et al., 2009) required a second rescue dose of naloxone (the second dose given IM). For a purpose-developed nasal naloxone spray, a more concentrated formulation of naloxone should be used, e.g. at least 5-10x current concentrations, a) to overcome the drug loss associated with administration of excessive volumes to the nasal cavity and b) to administer naloxone across the recommended dose range (i.e. bioequivalent to 0.4-2mg IV or IM).

A significant positive development in this regard is the recent FDA approval of a new nasal spray formulation of a concentrated naloxone solution (US territory only) (FDA, 2015). Pharmacokinetics data (including dose-equivalence and constancy) on concentrated naloxone nasal spray will hopefully become available, and it will be important to field-test the new product to assess the potential significance of practical obstacles, e.g., inter-individual variability, impact of airway blockage or apnea, impact of vomitus in the nasal passages or mouth, impact of nasal mucosal damage from drug abuse. This is necessary because drug users, may have damaged nasal mucosa – for example, ulceration, scarring and loss of tissue from repeated cocaine use (Peyrière et al., 2013). Absorption may consequently vary substantially between individuals, making it difficult to achieve systemic drug levels rapidly and reliably. There is also the possibility of interference with nasal absorption from vomiting associated with the overdose, thereby rendering the nasal cavity compromised.

5.3.5 Sublingual naloxone

The sublingual and buccal (from the oral vestibular cavity) routes both drain into the internal jugular vein via the facial veins, and thence rapidly to the brain (Pather, Rathbone, & Senel, 2008; Standring, 2015; Sudhakar, Kuotsu, & Bandyopadhyay, 2006). An FDA product application was submitted in 2015 for a sublingual naloxone spray (FDAnews, 2015). If the naloxone were to be absorbed rapidly and efficiently, then this could be viable. However, there are several concerns regarding the suitability of the sublingual route for the emergency administration of naloxone. Access to the mucosa under the tongue may be obstructed if the mouth of the overdose victim is closed and/or if vomiting has occurred. A sublingual spray would be difficult to administer, as liquid may be lost to swallowing. Sublingual tablets are typically small and would be hard to position. Furthermore, there was significant inter-subject variability of sublingual

naloxone delivery and effect in a pharmacodynamics study in opioid users (Preston et al., 1990).

5.3.6 Buccal naloxone

With buccal administration, a drug is absorbed across the buccal mucosa, a 40-50 cell (500-600 μm) thick stratified epithelium (Kulkarni et al., 2009). The vasculature of the buccal mucosa drains into the retromandibular, lingual and facial veins, which in turn drain directly into the internal jugular vein and, via the superior vena cava, into the systemic circulation (Pather et al., 2008; Sattar et al., 2014; Sudhakar et al., 2006).

No human in vivo data for buccal naloxone has been published to date. However, a working prototype lyophilized tablet of naloxone has been developed in collaboration between the Addictions Department and the Institute of Pharmaceutical Science at King's College London. The tablet is suitable for application to the buccal mucosa with rapid drug release for absorption (e.g. within 30 seconds) (Alqurshi et al., 2016). The development of this tablet and its in vitro properties are discussed in Chapter 9.

5.4 Discussion

5.4.1 Statement of principal findings

The development of non-injectable formulations of naloxone is of major importance because of the potential for administration by non-medical people in emergency situations. Injectable routes work well and are fit for purpose for use by medical staff in hospital settings or by ambulance personnel attending a community emergency overdose scenario. However, the consideration is different for emergency administration by the general public (i.e. without medical training). While family members can be trained and are regularly given such training and emergency injectable medications for other potential medical crises (e.g. adrenaline/epinephrine for allergy anaphylaxis, insulin for diabetics, etc.), there would nevertheless be greater ease of distribution and comfort with emergency administration if an effective and reliable non-injectable formulation of naloxone was available.

Examination of the extensive list of more than 100 different routes of administration identified three plausible non-injectable routes – nasal, sublingual and buccal - which

warrant proper study. If successful, all three routes could become viable, cost-effective future alternatives to the licensed naloxone injection and could facilitate effective bystander response to opioid-overdose while minimizing associated risk.

Consideration and investigation of nasal naloxone is the more advanced area. After a decade of community provision of improvised naloxone nasal spray, several pharmaceutical companies have recently been developing and testing purpose-made naloxone nasal sprays, and the FDA approved a first concentrated naloxone nasal spray in late 2015 (FDA, 2015) (see Chapter 4).

Sublingual medications have been used in medicine to great benefit in emergency situations, such as glyceryl trinitrate (GTN) sublingual tablets or spray as acute treatment of angina or myocardial infarct. However, the sublingual route may be compromised if there is vomit or secretions. In October 2015, FDA granted fast-track review to a new drug application for a sublingual naloxone spray (FDAnews, 2015).

No human data exist for buccal naloxone to date, and study of the buccal route for naloxone administration is less advanced. However, the buccal route has been successfully used to develop non-injectable versions of other medications previously available as injection only, such as buccal midazolam (Dale et al., 2006; Knoester et al., 2002; Schwagmeier, Alincic, & Striebel, 1998; Taylor, Okocha, Paton, Smith, & Connolly, 2008). There have also been promising experimental results with buccal naltrexone delivery in humans (Paderni et al., 2013). The potential of a lyophilized naloxone tablet for buccal administration is discussed in Chapter 9.

5.4.2 Strengths and weaknesses of the chapter

The main strength of this chapter lies in the methodological approach of its exhaustive consideration of all FDA-recognized routes of administration. However, it cannot be ruled out the possibility that other non-injectable routes that may in future prove feasible for naloxone administration due to technological advances. The scope of this chapter is further limited by the lack of empirical data from pre-clinical or clinical studies, which reflects the lack of investment in naloxone product development by science and by the pharmaceutical industry.

5.4.3 Possible mechanisms and implications for clinicians

With regard to feasibility of the three candidate routes (see also Table 15) and their suitability for clinical practice, I consider the nasal route to be strong if concentrated solutions are used and provided dose-titration schedules can be made possible. I consider the sublingual route to be weakest, given that access to the sublingual mucosa may be obstructed in at least two scenarios: a) if the mouth of the overdose victim is closed and/or b) if vomiting has occurred. I consider the buccal route to hold real potential if rapid absorption and good stability can be achieved.

5.5 Conclusion

Take-home naloxone provision is held back by reliance on injectable formulations. Improvised nasal naloxone kits have been distributed in many communities, but their clinical safety is unknown (see Chapter 4).

Alternative non-injectable naloxone products need to be explored. From application of the FDA criteria and review of all 112 categories for routes of administration, only three candidate routes for non-injectable naloxone administration were identified: Nasal, sublingual and buccal. A first concentrated nasal spray was granted FDA approval in 2015.

Despite these recent advances, my systematic review in this chapter illustrates that only limited pharmacokinetic data for non-injectable naloxone have been made available in the peer-reviewed domain. In the next chapter, I aim to address this gap by reviewing relevant naloxone data published by academia and pharmaceutical industry in international patent applications.

Table 16 First stage of selection process: FDA list (1992) and exclusion criteria

			Exclusion criteria				
NAME	**DEFINITION**	**FDA Code**	**Injectable/ Invasive** *has primacy*[1]	**Requires medical training**	**Not publically acceptable**	**Insufficient systemic absorption**	**No rapid effect**
AURICULAR (OTIC)	Administration to or by way of the ear.	013				X	X
BUCCAL	Administration directed toward the cheek, generally from within the mouth.	030					
CONJUNCTIVAL	Administration to the conjunctiva, the delicate membrane that lines the eyelids and covers the exposed surface of the eyeball.	068				X	X
CUTANEOUS	Administration to the skin.	130				X	X
DENTAL	Administration to a tooth or teeth.	038				X	X
ELECTRO-OSMOSIS	Administration of through the diffusion of substance through a membrane in an electric field.	357		X			
ENDOCERVICAL	Administration within the canal of the cervix uteri (synonymous with the term intracervical).	131	**X**				
ENDOSINUSIAL	Administration within the nasal sinuses of the head.	133		?			
ENDOTRACHEAL	Administration directly into the trachea.	401		X			
ENTERAL	Administration directly into the intestines.	313				X	
EPIDURAL	Administration upon or over the dura mater.	009	**X**				
EXTRA-AMNIOTIC	Administration to the outside of the membrane enveloping the fetus	402	**X**				
EXTRACORPOREAL	Administration outside of the body.	057					X
HEMODIALYSIS	Administration through hemodialysate fluid.	140	**X**				

NAME	DEFINITION	FDA Code	Exclusion criteria				
			Injectable/ Invasive *has primacy*[1]	Requires medical training	Not publically acceptable	Insufficient systemic absorption	No rapid effect
INFILTRATION	Administration that results in substances passing into tissue spaces or into cells.	361	X				
INTERSTITIAL	Administration to or in the interstices of a tissue.	088	X				
INTRA-ABDOMINAL	Administration within the abdomen.	056	X				
INTRA-AMNIOTIC	Administration within the amnion.	060	X				
INTRA-ARTERIAL	Administration within an artery or arteries.	037	X				
INTRA-ARTICULAR	Administration within a joint.	007	X				
INTRABILIARY	Administration within the bile, bile ducts or gallbladder.	362	X				
INTRABRONCHIAL	Administration within a bronchus.	067	X				
INTRABURSAL	Administration within a bursa.	025	X				
INTRACARDIAC	Administration with the heart.	027	X				
INTRACARTILAGINOUS	Administration within a cartilage; endochondral.	363	X				
INTRACAUDAL	Administration within the cauda equina.	413	X				
INTRACAVERNOUS	Administration within a pathologic cavity, such as occurs in the lung in tuberculosis.	132	X				
INTRACAVITARY	Administration within a non-pathologic cavity, such as that of the cervix, uterus, or penis, or such as that which is formed as the result of a wound.	023	X				
INTRACEREBRAL	Administration within the cerebrum.	404	X				

NAME	DEFINITION	FDA Code	Exclusion criteria				
			Injectable/ Invasive *has primacy*[1]	Requires medical training	Not publically acceptable	Insufficient systemic absorption	No rapid effect
INTRACISTERNAL	Administration within the cisterna magna cerebellomedularis.	405	X				
INTRACORNEAL	Administration within the cornea (the transparent structure forming the anterior part of the fibrous tunic of the eye).	406	X				
INTRACORONAL, DENTAL	Administration of a drug within a portion of a tooth which is covered by enamel and which is separated from the roots by a slightly constricted region known as the neck.	117	X				
INTRACORONARY	Administration within the coronary arteries.	119	X				
INTRACORPORUS CAVERNOSUM	Administration within the dilatable spaces of the corporus cavernosa of the penis.	403	X				
INTRADERMAL	Administration within the dermis.	008	X				
INTRADISCAL	Administration within a disc.	121	X				
INTRADUCTAL	Administration within the duct of a gland.	123	X				
INTRADUODENAL	Administration within the duodenum.	047	X				
INTRADURAL	Administration within or beneath the dura.	052	X				
INTRAEPIDERMAL	Administration within the epidermis.	127	X				
INTRAESOPHAGEAL	Administration within the esophagus.	072	X				
INTRAGASTRIC	Administration within the stomach.	046	X				
INTRAGINGIVAL	Administration within the gingivae.	307	X				

			Exclusion criteria				
NAME	**DEFINITION**	**FDA Code**	**Injectable/ Invasive** *has primacy*[1]	**Requires medical training**	**Not publically acceptable**	**Insufficient systemic absorption**	**No rapid effect**
INTRAILEAL	Administration within the distal portion of the small intestine, from the jejunum to the cecum.	365	**X**				
INTRALESIONAL	Administration within or introduced directly into a localized lesion.	042	**X**				
INTRALUMINAL	Administration within the lumen of a tube.	310	**X**				
INTRALYMPHATIC	Administration within the lymph.	352	**X**				
INTRAMEDULLARY	Administration within the marrow cavity of a bone.	408	**X**				
INTRAMENINGEAL	Administration within the meninges (the three membranes that envelope the brain and spinal cord).	409	**X**				
INTRAMUSCULAR	Administration within a muscle.	005	**X**				
INTRAOCULAR	Administration within the eye.	036	**X**				
INTRAOVARIAN	Administration within the ovary.	354	**X**				
INTRAPERICARDIAL	Administration within the pericardium.	314	**X**				
INTRAPERITONEAL	Administration within the peritoneal cavity.	004	**X**				
INTRAPLEURAL	Administration within the pleura.	043	**X**				
INTRAPROSTATIC	Administration within the prostate gland.	061	**X**				
INTRAPULMONARY	Administration within the lungs or its bronchi.	414	**X**				
INTRASINAL	Administration within the nasal or periorbital sinuses.	010	**X**				
INTRASPINAL	Administration within the vertebral column.	022	**X**				

NAME	DEFINITION	FDA Code	Exclusion criteria				
			Injectable/ Invasive *has primacy*[1]	Requires medical training	Not publically acceptable	Insufficient systemic absorption	No rapid effect
INTRASYNOVIAL	Administration within the synovial cavity of a joint.	019	**X**				
INTRATENDINOUS	Administration within a tendon.	049	**X**				
INTRATESTICULAR	Administration within the testicle.	110	**X**				
INTRATHECAL	Administration within the cerebrospinal fluid at any level of the cerebrospinal axis, including injection into the cerebral ventricles.	103	**X**				
INTRATHORACIC	Administration within the thorax (internal to the ribs); synonymous with the term endothoracic.	006	**X**				
INTRATUBULAR	Administration within the tubules of an organ.	353	**X**				
INTRATUMOR	Administration within a tumor.	020	**X**				
INTRATYMPANIC	Administration within the aurus media.	366				X	X
INTRAUTERINE	Administration within the uterus.	028	**X**				
INTRAVASCULAR	Administration within a vessel or vessels.	021	**X**				
INTRAVENOUS	Administration within or into a vein or veins.	002	**X**				
INTRAVENOUS BOLUS	Administration within or into a vein or veins all at once.	138	**X**				
INTRAVENOUS DRIP	Administration within or into a vein or veins over a sustained period of time.	137	**X**				
INTRAVENTRICULAR	Administration within a ventricle.	048	**X**				
INTRAVESICAL	Administration within the bladder.	128	**X**				
INTRAVITREAL	Administration within the vitreous body of the eye.	311	**X**				

			Exclusion criteria				
NAME	**DEFINITION**	**FDA Code**	**Injectable/ Invasive** *has primacy*[1]	**Requires medical training**	**Not publically acceptable**	**Insufficient systemic absorption**	**No rapid effect**
IONTOPHORESIS	Administration by means of an electric current where ions of soluble salts migrate into the tissues of the body.	055		X			
IRRIGATION	Administration to bathe or flush open wounds or body cavities.	032		X		X	
LARYNGEAL	Administration directly upon the larynx.	364	**X**				
NASAL	Administration to the nose; administered by way of the nose.	014					
NASOGASTRIC	Administration through the nose and into the stomach.	071		X	X		
NOT APPLICABLE	Routes of administration are not applicable.	312	N/A	N/A	N/A	N/A	N/A
OCCLUSIVE DRESSING TECHNIQUE	Administration by the topical route which is then covered by a dressing which occludes the area.	134				X	X
OPHTHALMIC	Administration to the external eye.	012				X	X
ORAL	Administration to or by way of the mouth.	001				X	
OROPHARYNGEAL	Administration directly to the mouth and pharynx.	410					
OTHER	Administration is different from others on this list.	135	N/A	N/A	N/A	N/A	N/A
PARENTERAL	Administration by injection, infusion, or implantation.	411	**X**				
PERCUTANEOUS	Administration through the skin.	113	**X**				
PERIARTICULAR	Administration around a joint.	045	**X**				
PERIDURAL	Administration to the outside of the dura mater of the spinal cord..	050	**X**				
PERINEURAL	Administration surrounding a nerve or nerves.	412	**X**				

NAME	DEFINITION	FDA Code	Exclusion criteria				
			Injectable/ Invasive *has primacy*[1]	Requires medical training	Not publically acceptable	Insufficient systemic absorption	No rapid effect
PERIODONTAL	Administration around a tooth.	040				X	X
RECTAL	Administration to the rectum.	016			X		
RESPIRATORY (INHALATION)	Administration within the respiratory tract by inhaling orally or nasally for local or systemic effect.	136					
RETROBULBAR	Administration behind the pons or behind the eyeball.	034	**X**				
RETROBULBAR	Administration behind the pons or behind the eyeball.	034	**X**				
SOFT TISSUE	Administration into any soft tissue.	109	**X**				
SUBARACHNOID	Administration beneath the arachnoid.	066	**X**				
SUBCONJUNCTIVAL	Administration beneath the conjunctiva.	096	**X**				
SUBCUTANEOUS	Administration beneath the skin; hypodermic.	003	**X**				
SUBLINGUAL	Administration beneath the tongue.	024					
SUBMUCOSAL	Administration beneath the mucous membrane.	053	**X**				
TOPICAL	Administration to a particular spot on the outer surface of the body.	011				X	X
TRANSDERMAL	Administration through the dermal layer of the skin to the systemic circulation by diffusion.	358				X	X
TRANSMUCOSAL	Administration across the mucosa.	122					
TRANSPLACENTAL	Administration through or across the placenta.	415	**X**				

			Exclusion criteria				
NAME	**DEFINITION**	**FDA Code**	**Injectable/ Invasive** *has primacy*[1]	**Requires medical training**	**Not publically acceptable**	**Insufficient systemic absorption**	**No rapid effect**
TRANSTRACHEAL	Administration through the wall of the trachea.	355		X	X	X	
TRANSTYMPANIC	Administration across or through the tympanic cavity.	124		X			X
UNASSIGNED	Route of administration has not yet been assigned.	400	N/A	N/A	N/A	N/A	N/A
UNKNOWN	Route of administration is unknown.	139	N/A	N/A	N/A	N/A	N/A
URETERAL	Administration into the ureter.	112		X		X	
URETHRAL	Administration into the urethra.	017		X	X	X	
VAGINAL	Administration into the vagina.	015			X		

Annotations: [1] If a route of administration required injection (or a similar invasive procedure), the route was automatically excluded. Vice versa, if a route did not involve injection (or a similar invasive procedure), the route was examined by means of the additional four exclusion criteria.

Chapter 6 Patent Applications for Non-Injectable Naloxone

Preface

In this chapter, I present a review of international research activity around the exploration of non-injectable naloxone formulations. My earlier systematic review of candidate routes for non-injectable naloxone administration (see Chapter 5) indicated that only limited human pharmacokinetic data of injection-free naloxone administration had been published in the peer-reviewed literature. To supplement what appeared to be scarce academic research output, I consequently needed to identify additional sources of information that would also capture research and development within pharmaceutical industry. An initial scoping search of the PatentScope database was promising and revealed a plenitude of information: depending on the sensitivity of the search method, the search term “naloxone” yielded between 522 and 19,000+ entries. The review presented in this chapter constitutes an attempt to access and analyze this information contained within the PatentScope database in a systematic and transparent manner to allow for potential future replication or application to other subject areas.

The content of this chapter has been accepted as first-authored manuscript (title: “International patent applications for non-injectable naloxone for opioid overdose reversal: Search and retrieve analysis of the PatentScope database”) for publication in Drug and Alcohol Review (in press) and was developed in collaboration with my PhD supervisor Professor Sir John Strang as well as Professor Ola Dale and Øyvind Danielsson Glende of The Norwegian University of Science and Technology (NTNU) in Trondheim. Professor Ola Dale is an anesthetist and clinical pharmacologist by training and heads a group of pain researchers at NTNU. Øyvind Danielsson Glende is a pharmacist who, as part of his graduate training, undertook a research visit at the National Addiction Centre at King’s College London in March 2016. At the time, he was enrolled in the Master of Science in Pharmacy course at NTNU (under supervision of Professor Dale). I supervised Øyvind during his research visit, and we jointly conducted the database searches, eligibility assessment, and data extraction from relevant records, as described in the Methods section of this chapter.

This chapter integrates pharmacokinetic data for intranasal and sublingual administration and reference routes (intramuscular, intravenous, subcutaneous) from five peer-reviewed journal articles (identified via PubMed) and three published international patent applications (identified via PatentScope). The original dataset of one of these three patent applications is presented and analyzed in Chapter 7.

6.1 Introduction

The previous chapter applied the FDA's 2012 criteria for non-injectable naloxone to the peer-reviewed literature and identified three candidate routes of administration for injection-free naloxone delivery: IN, sublingual, and buccal. On November 18, 2015, the FDA gave regulatory approval for a concentrated intranasal (IN) naloxone spray (NARCAN®) by Adapt (FDA, 2015), which constitutes the first-ever licensed non-injectable naloxone product (see also Chapter 4).

However, at the time of the FDA approval of the novel product, no results from clinical trials were published, and human PK data were only reported in one peer-reviewed publication for an improvised IN naloxone spray formulation (2mg/5ml), with extremely low absolute bioavailability (F=4%) relative to the intravenous reference (Dowling et al., 2008). Uncertainties regarding the viability of improvised, off-label IN spray (administered by attaching a mucosal atomizer device to a pre-filled naloxone syringe) for opioid overdose reversal have been described in Chapter 4 and primarily concern its non-response rate and lack of safety data.

This chapter attempts to close the gap in the literature by examining published international patent applications of non-injectable naloxone formulations and contributory PK data. The aims are threefold:

- Aim 1: To trace the concept and product development by route of administration;
- Aim 2: To describe the non-injectable naloxone formulations for which human in vivo data are available;
- Aim 3: To compare human PK data reported in the patent applications.

6.2 Methods

A three-stage approach has been taken.

6.2.1 Stage 1

The PatentScope database of the World Intellectual Property Organization (WIPO), which contains 58 million patent documents including 3 million published international patent applications (WIPO, 2016), was searched for patent applications for non-injectable naloxone formulations. PatentScope was searched for English-language patent applications ("Language: EN") that were registered with any international patent office ("Office(s): all") and contained the search term "naloxone" within their First Page

(default). Only patent applications for non-injectable naloxone that contained human PK data were eligible for inclusion in the analysis (Aims 2 & 3).

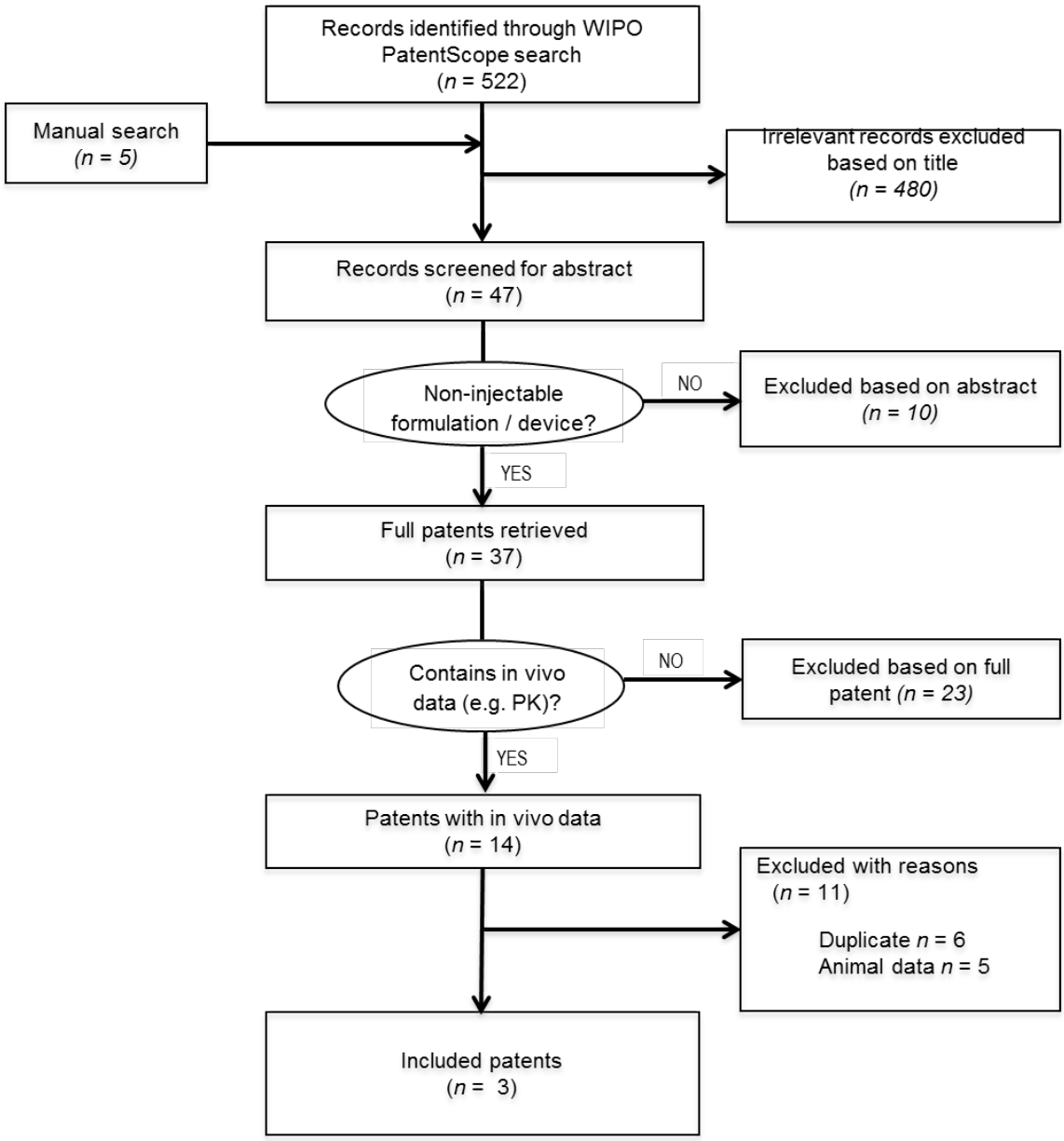

Figure 20 PRISMA diagram of PatentScope search

Table 17 Search protocol

Research question	**What are the pharmacokinetics of naloxone administration by the nasal, sublingual, or buccal routes of administration?** Aim: To assess the absorption of non-injectable naloxone formulations in humans
Search strategy	**Electronic Databases:** PubMed to identify relevant peer-reviewed articles published in English language between January 1946 and March (2nd week) 2016. **Search query:** "(nasal OR intranasal OR nose OR buccal OR sublingual) AND naloxone AND pharmacokinetics" **Query Translation:** ("nose"[MeSH Terms] OR "nose"[All Fields] OR "nasal"[All Fields]) OR intranasal[All Fields] OR ("nose"[MeSH Terms] OR "nose"[All Fields]) OR buccal[All Fields] OR ("administration, sublingual"[MeSH Terms] OR ("administration"[All Fields] AND "sublingual"[All Fields]) OR "sublingual administration"[All Fields] OR "sublingual"[All Fields]) AND ("naloxone"[MeSH Terms] OR "naloxone"[All Fields]) AND ("pharmacokinetics"[Subheading] OR "pharmacokinetics"[All Fields] OR "pharmacokinetics"[MeSH Terms]) **Hand-search:** The reference lists of relevant studies identified via PubMed were manually searched for additional studies meeting the below eligibility criteria.
General search filter used	Identify records from title, abstract, keywords; Map term to Medical Subject Heading Publication Year: 1946 – Current Duplicate articles to be removed using EndNote software version X6 for Windows.
Search Date	1 January 1946 to March (2nd week) 2016
Eligibility criteria	
• Population	Humans
• Intervention	Naloxone administration (in vivo)
• Comparison	Parenteral naloxone administration (if available)
• Outcomes	Pharmacokinetics data
• Study design	Clinical studies (randomized or observational trials)
• Publication status	Original studies published in peer-reviewed journals
Exclusion criteria	Case reports Qualitative studies Preclinical data Not reporting on naloxone Not reporting primary research data
Analysis method	Narrative synthesis

6.2.2 Stage 2

The pharmaceutical properties of the non-injectable naloxone formulations and human PK data were extracted from patent the applications. To improve comparability between formulations, dose-adjusted values per 1mg were generated.

6.2.3 Stage 3

To supplement and cross-check the data obtained in Stages 1 and 2, we also searched PubMed for human PK data for non-injectable naloxone using the Boolean search query "(nasal OR intranasal OR nose OR buccal OR sublingual) AND naloxone AND pharmacokinetics" (see Table 17 for search protocol). These three routes of administration were chosen based on the systematic review in Chapter 5 (Strang, McDonald, Alqurshi, et al., 2016).

6.3 Results

6.3.1 Stage 1

A PRISMA flow diagram of the selection process of patent applications is shown in Figure 20. 522 PatentScope records were identified using the search term "naloxone" for front-page matches. At this stage, a cross-check was made for known patent applications, and it was found that no entry for the FDA-approved Adapt IN spray product (NARCAN®, see also Chapter 4) had been captured. We thus additionally searched PatentScope for "Adapt OR Lightlake"-related entries. (In late 2014, Adapt had bought the global license from Lightlake Therapeutics Inc. to develop and commercialize their IN naloxone spray (PRNewsWire, 2014).) After matching for the search term "Lightlake" (front-page search, English language, all patent offices), this additional search yielded five patent applications, which had not been captured using the search term "naloxone" because Lightlake had not included the word 'naloxone' on the front page. Consequently, these five Lightlake patent applications were manually added (*n.b.* in the remainder of this chapter, I denote these as 'Lightlake' unless I refer directly to the licensed Adapt nasal spray product).

Of the 47 records that remained after removing 480 irrelevant records, 10 were excluded based on their abstract (e.g. active ingredient other than naloxone). The remaining 37 records were downloaded for full-text review and screened for human PK data. Of the

14 patent applications that contained relevant PK data, 11 were excluded for the following reasons: 5 reported only animal data, and 6 were duplicates (earlier or later versions of patents containing the same PK data but different patent claims or country of publication). Three published international patent applications were identified as eligible for inclusion: WO/2015/136373, WO/2015/095644, and WO/2012/156317. A timeline of the publication of all 37 patent applications (including excluded records) is provided as Table 20.

The timeline shows that the concept of IN naloxone (drops, spray, solution, suspension, ointment or gel) was first being explored at the University of Kentucky, with first animal data reported in 1982. The 1990s showed no activity for IN naloxone except for the patent application of a spray dispenser by Britannia Pharmaceuticals in 2000 (*n.b*. the same spray device as in the 2015 FDA-approved Adapt naloxone spray which uses the Aptar single unit-dose device, see Chapter 4). In 2005, an IN naloxone powder was proposed by the Chinese PLA Academy of Military Science. The first human PK data for IN naloxone were filed by Euro-Celtique in 2012 (WO/2012/156317).

The first patent application describing the concept of sublingual or buccal naloxone was published by the Israeli company Pentach Pharmaceuticals in 2004, and patent applications covering sublingual naloxone (spray, dripping pills) by two Beijing-based companies followed in 2007 and 2011. In 2012, Euro-Celtique included sublingual PK data in its patent application on concentrate IN naloxone spray (see above). In June 2015, INSYS Pharma submitted two patent applications for sublingual naloxone spray (no PK data) and was granted FDA fast-track review later that year (FDAnews, 2015).

6.3.2 Stage 2

Description of intranasal pharmacokinetic data

The following section summarizes the IN PK data reported in the published international patent applications WO/2015/136373 (Lightlake Therapeutics), WO/2015/095644 (AntiOp), and WO/2012/156317 (Euro-Celtique). All data were obtained using crossover study designs, though sample sizes differed from 7 to 35 subjects per arm. For a full summary of the PK data (including reference routes), please see Table 19.

AntiOp described two studies, which are hereby referred to as ‘Trial 1 (Pilot’) and ‘Trial 2’. AntiOp tested a 10mg/ml IN formulation administered as 0.1ml into one and two nostrils, as well as 0.2ml per nostril (0.1+0.1ml with 5-minute interval). Trial 1 (Pilot) also tested non-concentrate 1mg/ml naloxone, with mucosal atomizer device (MAD) attached

to a syringe, thus replicating the improvised IN naloxone distributed off-label in several countries.

Lightlake presented results from two studies: Study 1 assessed a 10mg/ml formulation, whereas Study 2 tested 20mg/ml and 40mg/ml formulations, all administered as 0.1ml into one and two nostrils (total volume: 0.2ml).

Euro-Celtique tested IN doses of 8mg (0.2ml per nostril; 20mg/ml concentration) and 16mg (0.2ml per nostril; 40mg/ml concentration). Euro-Celtique also included a sublingual arm (16mg/ml solution), but this route is not described here in detail, as its absolute bioavailability was only 1%.

For IN administration, absolute bioavailability (F; relative to intravenous) as well as relative bioavailability (F_{IM}; relative to intramuscular) are presented, as neither measure was reported across all three patent applications. (Euro-Celtique only provided F, whereas the more recent AntiOp and Lightlake patent applications reported F_{IM} in accordance with guidance from FDA).

F: For the Euro-Celtique data, I calculated F values of 22% (20mg/ml, administered as 0.2ml per nostril) and 21% (40mg/ml; 0.2ml per nostril) using $AUC_{0-\infty}$ data listed in the PK data appendix of the patent application. I was unable to obtain the higher F values of 32% (20mg/ml formulation) and 27% (40mg/ml) which Euro-Celtique cited in-text for lower doses (1.2 and 1.6mg, dose-adjusted from 8 and 16mg) in the body of the patent application. AntiOp only reported F_{IM}, but included an IV reference in Trial 1 (Pilot), which allowed me to manually determine the following F-values for comparison: 36% (0.1ml, one nostril only) and 42% (0.1ml per nostril) for the 10mg/ml formulation, and 11% for non-concentrate naloxone (1mg/ml per nostril).

F_{IM}: Lightlake achieved the highest F_{IM} values across all three patent applications, with 0.1ml of the 10mg/ml formulation administered into both nostrils (F_{IM}=57%). F_{IM} was lower (48%), when the volume of the same formulation was doubled (0.2ml per nostril). For the 20mg/ml formulation, F_{IM} was 54% (0.1ml, one nostril only) and 55% (0.1ml per nostril). The 40mg/ml formulations achieved 49% and 45% when administered into one and both nostrils, respectively. AntiOp reported the following F_{IM} values for a 10mg/ml formulation: 34% (0.1ml, one nostril only), 31-39% (0.1ml per nostril), and 26% (0.1ml per nostril, with re-administration after 5 minutes; i.e. total volume of 0.2ml per nostril). Non-concentrate naloxone (1mg/ml per nostril) had a F_{IM} of 10%.

$t_{1/2}$: The terminal half-life ($t_{1/2}$) is the time it takes for the blood concentration of a pharmacological agent to decrease by 50%, which usually translates into the loss of half of its pharmacologic activity. Euro-Celtique reported the longest terminal half-lives

($t_{1/2}$) for IN administration, with 9.1 (40mg/ml) and 9.5 hours (20mg/ml), though data were only available for 4 subjects. In the AntiOp and Lightlake patent applications, $t_{1/2}$ fell in the range of 1.2–2.1 hours.

t_{max}: IN t_{max} values ranged from 0.27 (AntiOp, 1mg/ml, 1ml per nostril) to 0.5 hours (AntiOp 10mg/ml, 0.1ml into one nostril and Lightlake 40mg/ml, 0.1ml into one nostril).

AUC & C_{max}: Dose-adjusted C_{max} values (per mg) were highest for the Lightlake 20mg/ml formulation administered as 0.1ml per nostril (C_{max}=1.66ng/ml). The same treatment arm achieved $AUC_{0-\infty}$=2.48ng*h/ml. The Euro-Celtique 20mg/ml formulation reached the highest $AUC_{0-\infty}$ value (2.76ng*h/ml) and dose-adjusted (per mg) C_{max} of 1.60ng/ml. The 1mg/ml non-concentrate AntiOp treatment (administered as 1ml per nostril) had the lowest values ($AUC_{0-\infty}$=0.45ng*h/ml; C_{max}=0.27ng/ml).

Additional exploratory analyses: In order to allow for examination of the potential influence of spray concentration on IN absorption, AUC, $C_{max,}$ and t_{max} values have been plotted against volume (adjusted by dose for AUC and C_{max}) and dose (see Figure 21). For both AUC and C_{max}, the plots indicate a positive association with dose and a negative association with the volume of the IN spray. The graphs do not suggest a clear association for t_{max}.

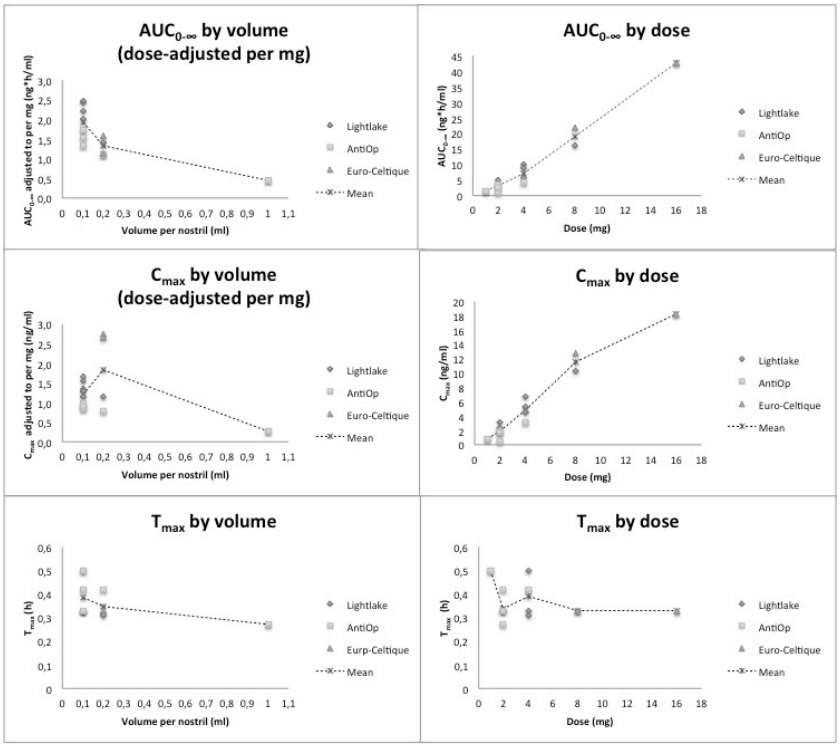

Figure 21 $AUC_{0-\infty}$, Cmax and tmax plotted by volume and dose

6.3.3 Stage 3

The PubMed search generated 56 matches, with zero duplicates (see Figure 22). 46 papers were excluded based on title and abstract (no primary data from in-human naloxone studies). The ten remaining records were downloaded for full text, with five papers excluded for the following reasons: one was a review article, and four did not include naloxone PK data (see Table 18 for a list of excluded studies). The remaining eligible five papers included human PK data in two papers for IN naloxone (Dowling et al., 2008; Middleton, Nuzzo, Lofwall, Moody, & Walsh, 2011) and three papers for sublingual naloxone (Fischer, Jonsson, & Hjelmstrom, 2015; Harris, Mendelson, Lin, Upton, & Jones, 2004; Nasser, Heidbreder, Liu, & Fudala, 2015). None of the papers contained human PK data for buccal naloxone.

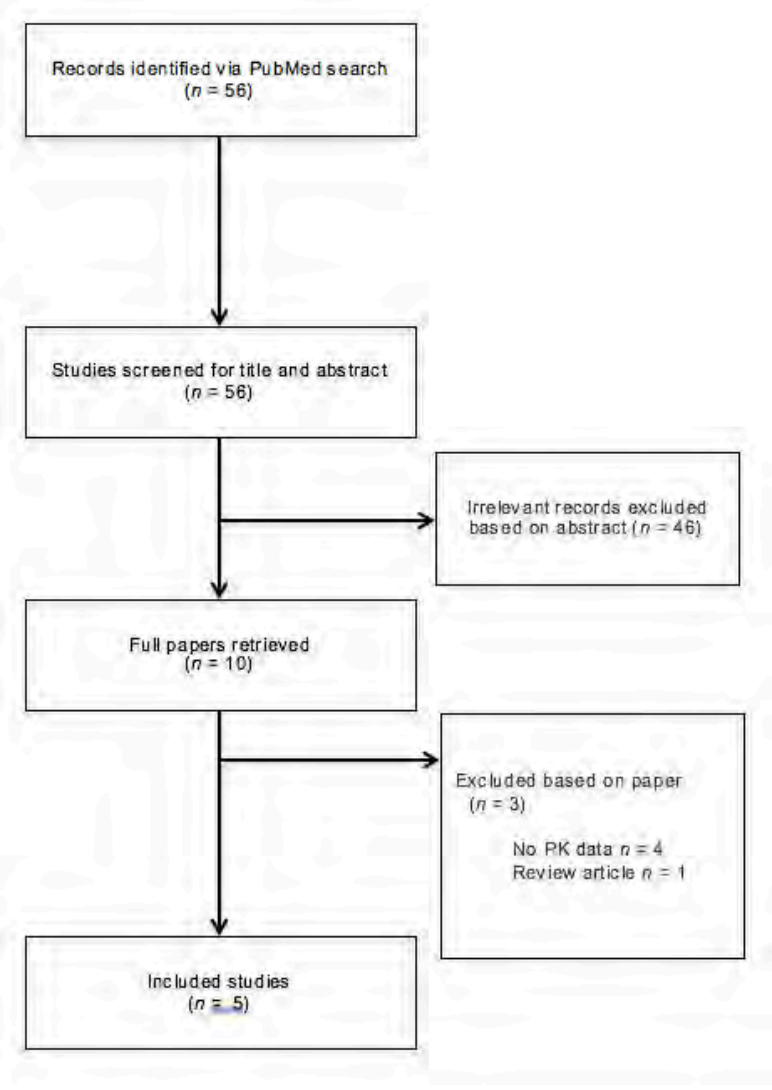

Figure 22 PRISMA diagram of PubMed search

Divergent bioavailability values have been reported for IN naloxone. One healthy volunteers study (n=6) assessed a non-concentrate formulation of IN naloxone (2mg/5ml) and reported an absolute bioavailability of only 4%, which the authors attributed as possibly due to the dilute solution (and high volume) used (Dowling et al., 2008). Higher absorption was reported in a study (Middleton et al., 2011) with recreational prescription opioid users (n=10) where absolute bioavailability of IN administration of crushed buprenorphine/naloxone (4:1 ratio) of two concentrations (0.5mg, 2mg naloxone) was 24% and 30%, respectively.

Systemic uptake after sublingual naloxone administration was generally found to be low. In one healthy volunteers study, naloxone doses of 1.4mg and 2mg were administered in combination with buprenorphine, resulting in a median t_{max} of 0.8h and peak naloxone plasma concentrations below 0.4ng/ml for both doses (Fischer et al., 2015). A second study in non-dependent opioid users (n=8) (Harris et al., 2004) assessed escalating naloxone doses (1mg, 2mg, 4mg) and found that dose-effect comparisons were impossible, as many naloxone plasma concentrations were below the level of quantification (0.050ng/ml). The highest individual AUC reported was 0.55ng*h/ml.

A third study (Nasser et al., 2015) suggested that sublingual naloxone bioavailability is negatively associated with healthy liver functioning. A sublingual 0.5mg naloxone tablet (in combination with 2mg buprenorphine) was administered to forty-three subjects stratified by hepatic impairment (mild, moderate, or severe), HCV diagnosis without hepatic impairment, and healthy volunteers. Across all groups, the median t_{max} ranged from 0.8-1.1 hours, with mean $t_{1/2}$ from 1.9-5.5 hours. However, the $AUC_{0\text{-last}}$ data revealed an approximate 3 to 14-fold increase in total naloxone exposure in subjects with moderate and severe hepatic impairment. Likewise, the naloxone C_{max} was 3 to 11-times higher in subjects with hepatic impairment.

Table 18 Excluded studies (n=5)

Study ID	DOI / URL	Source	Reason for exclusion
Chiang (2003)	10.1016/S0376-8716(03)00058-9	PubMed	Review article
Ciraulo (2006)	10.1177/0091270005284192	PubMed	No naloxone PK data
Compton (2006)	10.1016/j.drugalcdep.2005.08.005	PubMed	No naloxone PK data
Compton (2007)	10.1097/ADM.0b013e31806dcc3e	PubMed	No naloxone PK data
Luo (2012)	10.1128/AAC.00077-12	PubMed	No naloxone PK data

6.4 Discussion

Human PK data for purpose-made non-injectable naloxone formulations had not been reported in peer-reviewed scientific papers at the time of FDA approval of the first IN naloxone spray (Krieter et al., 2016). However, recent published international patent applications by the companies AntiOp, Euro-Celtique and Lightlake contain data on concentrated sublingual and IN spray formulations in the range 10-40mg/ml. This chapter integrates data from WIPO PatentScope with scientific publications retrievable via PubMed, charting R&D activity over two decades (particularly 2012-present).

6.4.1 Statement of principal findings

Across all concentrate IN naloxone formulations, bioavailability was 21-42% relative to IV and 26-57% relative to IM. Plotting of the $AUC_{0-\infty}$ and C_{max} values showed a moderately linear relationship with dose (higher dose → higher $AUC_{0-\infty}$, C_{max}) and a negative association for volume (lower volume → higher $AUC_{0-\infty}$, C_{max}). The highest IN bioavailability (F_{IM}=57%) was reached when 0.1ml of a 10mg/ml formulation was administered into both nostrils. For the same formulation, F_{IM} decreased to 48% when volume doubled to 0.2ml per nostril. Volume clearly matters. Dose-concentration linearity is also evident. The importance of (low) volume is underlined by the observation that IN bioavailability was drastically lower (F=11%) when a non-concentrated formulation of 1mg/ml was administered into both nostrils. This confirms previous reports of low bioavailability (F=4%) for dilute IN spray (0.4mg/ml) (Dowling et al., 2008). A non-concentrated solution is more likely to lead to a proportion being swallowed, as a larger volume would be expected to run out of the nasopharynx, rather than being absorbed from the nasal mucosa. This would be expected to lower the systemic availability due to first-pass metabolism of naloxone absorbed from the gastrointestinal tract.

Sublingual naloxone administration of a concentrate solution (16mg/ml) had very low bioavailability (F=1%). This is below the range of 7-9% identified by Chiang et al. in their review of sublingual buprenorphine-naloxone formulations (Chiang & Hawks, 2003). Sublingual is thus unlikely to be a route of administration of clinical value.

6.4.2 Strengths and weaknesses of the chapter

The methodology of this review of non-injectable concentrate naloxone formulations is novel in that it includes examination of public-domain information from patent applications. A core strength of this analysis lies in the integration of empirical evidence

from PubMed and WIPO PatentScope databases, capturing both academic and pharmaceutical industry advances in the field.

The validity of this comparison of IN PK data across different patent applications is strengthened by the similarity of the IN spray formulations used. While Euro-Celtique only disclosed dose concentrations, all formulations all formulations by Lightlake and AntiOp with provided PK data are characterized by absence of absorption enhancers (which increase membrane permeation) and viscosity-increasing agents (which increase the residence time of naloxone to the nasal mucosa and thus contributes to better absorption).

Potential limitations need to be considered. Firstly, not all research and development activity leads to registration of intellectual property or to journal publication, and non-significant or negative results have low likelihood of getting published. Secondly, data published in patent applications has not undergone peer-review, and data quality is thus dependent on the patent applicant. Thirdly, the WIPO PatentScope database search was unlikely exhaustive. Considering that the search initially failed to capture the Lightlake patent applications, the possibility of other false-negatives cannot be ruled out. I conducted the default “First Page” search, which identified any patent document with the search term (“naloxone”) mentioned on its cover page, generating 522 matches. Had I conducted the more comprehensive “Full Text” search (“naloxone” mentioned in any full-text patent document), PatentScope would have identified over 19,000 matches, which would have exceeded my capacity for manual screening. Compared to online literature databases such as PubMed or Embase, the functionality of the PatentScope interface is less advanced, in that users cannot export full search results to a citation manager. For every PatentScope entry, we thus had to associated documents had to be downloaded individually to allow for assessment of eligibility for inclusion in the analysis. I considered supplementing the PatentScope search with additional query of all national and regional patent offices for which our PatentScope “naloxone” search had yielded relevant entries (Canada, China, European Union, Germany, Great Britain, Israel, Russia, Singapore, South Africa, US; see Table 20). However, I concluded that this was not feasible due to their different search and output formats that are not always compatible with PatentScope: for instance, the British online database Ipsum of the UK Intellectual Property office only permits search by application or publication number (i.e. not by keyword, e.g. “naloxone”) (IPO, 2016), and the US Patent and Trademark Office offers two separate search modes: one for patent applications (Patent Application Full-Text and Image Database, AppFT) and one for issued patents (Patent Full-Text and Image

Database; PatFT) (USPTO, 2016), whereas PatentScope does not provide such distinction.

The fourth limitation concerns the quality of the data retrieved: PatentScope records typically do not include raw data, and this analysis was reliant upon summary data provided by the patent applicants. Consequently, the comparability of the PK results was limited by different analytical methods and result formats used in the individual studies included in the patent applications (e.g. bioavailability reported as F vs. F_{IM}; central tendency expressed as mean vs. median). For instance, the actual concentration of the AntiOp formulation (10mg/ml Naloxone HCl or 10mg/ml Naloxone HCl dihydrate) remains uncertain, which could have affected calculation of dose-adjusted values in Table 19. There was also variability in the sampling periods (8-36 hours), which may have impacted AUC-dependent measures (e.g. F%, F_{IM}%). In terms of reliability of the mean values reported in Table 19, it also needs to be borne in mind that the crossover studies (which comprised pilot and registration trials) differed substantially in sample sizes (7-35 subjects per treatment arm).

6.4.3 Possible mechanisms and implications for clinicians

These findings have multiple implications for clinicians and policymakers.

IN naloxone: Low spray volume and high concentrations lead to better IN naloxone absorption. Concentrated IN naloxone spray is thus a potentially valuable non-injectable formulation for opioid overdose reversal. This is likely relevant both in medical settings and in the community (take-home naloxone programs). This conclusion accords with the first FDA approval of an IN naloxone spray product (FDA, 2015), at 4mg/0.1ml naloxone hydrochloride (i.e. 40mg/ml concentration).

However, further examination is required of the full PK curve and the resulting clinical effect: for all doses of the 40mg/ml formulations tested (4-16mg), C_{max} (5.34-18.3ng/ml) was much higher than for intramuscular (IM) references (C_{max}=0.77-1.05ng/ml). Consequently, while clinical efficacy of concentrated IN sprays is likely, there is the risk of inducing acute opioid withdrawal in overdose victims (Buajordet et al., 2004). A recent qualitative analysis of heroin/opioid overdose reversals found instances of apparent excessive naloxone dosing and consequent ‘over-antagonism’, sometimes triggering discharge and active further drug-seeking (Neale & Strang, 2015). Hepatic impairment also increases naloxone bioavailability, particularly relevant when larger fractions of buccal/sublingual or IN naloxone are swallowed (Nasser et al., 2015), potentially causing distress and adverse events from naloxone over-antagonism in dependent patients.

Sublingual naloxone: In October 2015, INSYS Therapeutics announced that its sublingual naloxone spray (formulation unknown) had been granted FDA fast-track review. Considering the low bioavailability reported by the Euro-Celtique study, it seems unlikely that sublingual naloxone will be clinically useful.

6.4.4 Questions for future research

Unanswered questions around non-injectable naloxone remain.

All PK data reported in the referenced patent applications were from healthy volunteers. It remains unclear how these findings relate to the heroin/opioid users where non-response rates (i.e. response judged by ambulance personnel to need supplementary injected dose) around 18–26% have been reported for IN naloxone (Kelly et al., 2005; Kerr et al., 2009).

Secondly, naloxone plasma concentrations required to reverse opioid overdose remain unknown. The therapeutic naloxone dose may even differ according to route of administration, alongside dose, potency, and half-life of the opioid agonist as well as inter-individual variability. This requires further study.

Thirdly, while the PK data from the patent applications indicated a negative relationship between volume and naloxone uptake, they did not allow us to determine a cut-off for IN spray volume (volumes above which naloxone is lost to pre or post-nasal drip). Definition of the maximum volume will affect repeat-administrations of IN naloxone spray. This too needs resolution.

Fourthly, the poor IN bioavailability of non-concentrated naloxone using the MAD device also raises important questions (Dale, 2016; Strang & McDonald, 2016; Strang, McDonald, Tas, & Day, 2016). From a scientific perspective, how can such low absorbed doses be effective if they are indeed succeeding in reversing overdose? Also, the continued use of improvised (i.e. dilute) IN naloxone kits needs review.

Finally, this chapter presents a new analytical method of synthesis of public patent data from the WIPO PatentScope database. The limitations discussed above illustrate that this method will require optimization and would benefit from enhanced functionality of the PatentScope interface, so that review of a greater volume of patent documents would become manageable. In future, such syntheses would also be more valuable if data were presented uniformly: this would require investigators of non-injectable naloxone formulations (including pharmaceutical companies) to publish their data even if findings are negative (see e.g. AllTrials.net) (Hawkes, 2012).

6.5 Conclusions

Over the past fifteen years, IN naloxone sprays have been tested in humans, but no product was licensed and commercially available until late 2015 (FDA, 2015). With an ongoing epidemic of prescription-opioid overdose deaths alongside a more recent rapid rise in heroin deaths, an IN naloxone spray is finally available to prevent overdose deaths in opioid users - a target population vastly underserved for decades. This first licensed non-injectable naloxone marks a significant milestone towards wider naloxone access and more effective prevention of opioid overdose deaths. High-concentrate IN naloxone has good bioavailability although, thus far, formal product testing has only involved healthy volunteers. It remains possible that high-concentrate formulations may provoke naloxone over-antagonism in opioid-dependent patients. Options for dose-titration and alternative routes (e.g. buccal, see Chapter 9) also need exploration. PK data for naloxone products need to be routinely published in the peer-reviewed domain: only then can there be properly informed consideration of different naloxone products by the clinical, policy and scientific communities.

I was able to obtain access to the original dataset of the 2012 Euro-Celtique patent application (WO/2012/156317), i.e. one of the three patent applications included in this chapter. My analysis of this original dataset is covered in Chapter 7.

Table 19 Pharmacokinetic properties of patent formulations

Route	Study	n	Conc. mg/ml	Nostrils #	Dose (mg)/ volume (ml)	F%	F_{IM}%	t_{max} (h)	$t_{1/2}$ (h)	Observed values			Dose-adjusted values (per mg)		
										C_{max} (ng/ml)	$AUC_{0-\infty}$ (ng*h/ml)	AUC_{0-last} (ng*h/ml)	C_{max} (ng/ml)	$AUC_{0-\infty}$ (ng*h/ml)	AUC_{0-last} (ng*h/ml)
IV	AntiOp Trial 1	13	0.4		0.4/1.0			*0.03±0.1*	*1.28±0.2*	*3.87±2.7*	*1.67±0.5*		*9.68*[a]	*4.18*[a]	
	Euro-Celtique	11	1		1.0/1.0			0.85±1.6	0.89±0.1[e]	17.9±29.9	12.6±12.4[e]	10.5±7.2	17.9[a]	12.6[a]	10.5[a]
IM	AntiOp Trial 1	13	NA		1.0/NA	106[a, d]		*0.33±0.5*	*1.41±0.3*	*2.54±1.0*	*4.43±1.2*		*2.54*[a]	*4.43*[a]	
	AntiOp Trial 2	34	0.4		0.4/1.0			*0.17 (0.1, 1.0)*	1.38±0.3	1.05±0.4	1.67±0.4		2.63[a]	4.18[a]	
	Lightlake 1	14	0.4		0.4/1.0			0.34±0.1	*1.21±0.2*	0.77±0.2	1.42±0.3	1.38±0.3	1.91[a]	3.55[a]	3.45[a]
	Lightlake 2	28	0.4		0.4/1.0			*0.42 (0.1, 2.0)*	1.19[b]	0.91±0.3	1.83±0.4	1.79±0.4	2.26±0.7	4.57±1.1	4.48[a]
SQ	AntiOp Trial 1	13	NA		1.0/NA	99[a, d]	94[a, d]	*0.17±0.3*	*1.59±0.6*	*2.72±0.8*	*4.15±1.1*		*2.72*[a]	*4.15*[a]	
IN	AntiOp Trial 1	13	10	2	2.0/0.2	42[a, d]	39[a, d]	*0.42±0.3*	*1.53±0.2*	*1.95±1.1*	*3.47±0.8*		*0.98*[a]	*1.74*[a]	
	AntiOp Trial 1	13	10	1	1.0/0.1	36[a, d]	34[a, d]	*0.50±0.2*	*1.41±0.3*	*0.84±0.5*	*1.52±0.5*		*0.84*[a]	*1.52*[a]	
	AntiOp Trial 1	7	1	2	2.0/2.0	11[a, d]	10[a, d]	*0.27±0.1*	*1.64±0.3*	*0.53±0.2*	*0.90±0.2*		*0.27*[a]	*0.45*[a]	
	AntiOp Trial 2	33	10	2	2.0/0.2		31[a, d]	*0.33 (0.3, 0.8)*	1.37±0.3	1.78±1.0	2.63±1.3		0.89[a]	1.32[a]	
	AntiOp Trial 2	35	10	2+2[c]	4.0/0.4		26[a, d]	*0.42 (0.2, 1.0)*	1.41±0.3	3.06±1.6	4.42±2.2		0.77[a]	1.11[a]	
	Lightlake 1	14	10	2	2.0/0.2		57	0.33±0.1	1.19±0.1	2.32±1.0	3.44±1.0	3.41±1.0	1.16[a]	1.72[a]	1.71
	Lightlake 1	14	10	2	4.0/0.4		48	0.31±0.1	1.22±0.1	4.55±2.9	5.68±1.6	5.63±1.6	1.14[a]	1.42[a]	1.41
	Lightlake 2	28	20	1	2.0/0.1		54	*0.33 (0.3, 1.0)*	1.70[b]	3.11±1.1	4.86±1.5	4.81±1.5	1.56±0.6	2.43±0.7	2.41
	Lightlake 2	28	20	2	4.0/0.2		55	*0.33 (0.1, 0.5)*	2.09[b]	6.63±2.3	9.91±2.7	9.82±2.7	1.66±0.6	2.48±0.7	2.46
	Lightlake 2	28	40	1	4.0/0.1		49	*0.50 (0.2, 1.0)*	2.00[b]	5.34±2.4	8.87±3.3	8.78±3.3	1.34±0.6	2.22±0.8	2.20
	Lightlake 2	28	40	2	8.0/0.2		45	*0.33 (0.2, 1.0)*	1.91[b]	10.3±4.0	16.1±3.8	15.9±3.8	1.29±0.5	2.01±0.5	1.99
	Euro-Celtique	11	20	2	8.0/0.4	22)[a, d]		0.34±0.2	9.48±3.9[f]	12.8±4.5	22.0±4.2[f]	20.1±4.9	1.60[a]	2.76[a]	2.51[a]
	Euro-Celtique	12	40	2	16.0/0.4	(21)[a, d]		0.39±0.2	9.09±2.7[f]	18.3±7.5	42.8±10.6[f]	32.8±10.2	1.14[a]	2.67[a]	2.05[a]
SL	Euro-Celtique	11	16		16.0/1.0	(1)[a, d]		3.91±10.6	1.13±0.2[f]	0.90±0.4	1.50±0.4[f]	2.67±1.8	0.06[a]	0.09[a]	0.17[a]

Annotations: Values for t_{max}, C_{max}, AUC, $t_{1/2}$ denote mean ±SD, except for values in italics. Values in italics denote median ±SD or median (min, max). Inconsistent information between the patent and the PK data whether the formulation contained10mg/ml Naloxone HCl dihydrate or 10mg/ml Naloxone HCl. Dose-adjusted values (per mg) in table are based on Naloxone HCl.
[a] calculated values; [b] harmonized mean; [c] re-administration after 5 minutes; [d] calculated F and F_{IM} values based on $AUC_{0-\infty}$; [e] sample size = 3; [f] sample size = 4; NA = not available; IV = Intravenous; IM = Intramuscular; SQ = Subcutaneous; IN = Intranasal; SL = Sublingual.

Table 20 Timeline of publication of patent applications

Year	Publication date	Number	Applicants	Title	Country	Exclusion
2016	14.01.2016	20160008349	Insys Pharma, Inc.	Sublingual naloxone spray	US	No PK data
	14.01.2016	WO/2016/007245	Insys Pharma, Inc.	Sublingual naloxone spray	WO	No PK data
2015	27.12.2015	2572217	N/A	Pharmaceutical composition in form of naloxone-hydrochloride-based nasal spray and method of obtaining thereof	RU	No PK data
	17.09.2015	WO/2015/136373	Lightlake Therapeutics, Inc.	Nasal drug products and methods of their use	WO	N/A
	17.09.2015	20150258019	Lightlake Therapeutics, Inc.	Nasal drug products and methods of their use	US	Duplicate
	27.08.2015	20150238420	Hélène REY	Naloxone mono-product and multi-layer tablet	US	No PK data
	25.06.2015	WO/2015/095644	AntiOp, Inc.	Intranasal naloxone compositions and methods of making and using same	WO	N/A
	25.06.2015	20150174061	AntiOp, Inc.	Intranasal naloxone compositions and methods of making and using same	US	Duplicate
	18.06.2015	WO/2015/086528	Develco Pharma Schweiz AG	Naloxone mono-product and multi-layer tablet	WO	No PK data
	07.05.2015	20150126540	Euro-Celtique S.A.	Intranasal Pharmaceutical Dosage Forms Comprising Naloxone	US	Duplicate
	15.01.2015	20150018379	Euro-Celtique S.A.	Intranasal Pharmaceutical Dosage Forms Comprising Naloxone	US	Duplicate
2014	30.07.2014	2013/08280	Euro-Celtique S.A.	Intranasal pharmaceutical dosage forms comprising naloxone	ZA	No PK data
	30.04.2014	103764119	Euro-Celtique S.A.*	Intranasal pharmaceutical dosage forms comprising naloxone	CN	Duplicate
	19.03.2014	2706982	Euro-Celtique S.A.	Intranasal pharmaceutical dosage forms comprising naloxone	EP	Duplicate
2013	30.12.2013	194927	Euro-Celtique S.A.	Intranasal pharmaceutical dosage forms comprising naloxone	SG	No PK data
2012	22.11.2012	WO/2012/156317	Euro-Celtique S.A.	Intranasal pharmaceutical dosage forms comprising naloxone	WO	N/A
	22.11.2012	2835940	Euro-Celtique S.A.	Intranasal pharmaceutical dosage forms comprising naloxone	CA	No PK data
2011	31.08.2011	102166198	Chongqing Jewelland Pharmaceutical Development	Stable naloxone hydrochloride freeze-dry preparation and preparation method	CN	No PK data
	06.04.2011	102000037	Beijing Shuanglu Lisheng Pharmaceutical Co.	Sublingual naloxone hydrochloride dripping pill	CN	Animal PK data only
2009	27.01.2009	2344822	N/A	Method of heroin addiction treatment	RU	No PK data

Year	Publication date	Number	Applicants	Title	Country	Exclusion
2007	24.10.2007	101057830	Beijing Tianchuan Junwei Medicine Technology Development Ltd.	Naloxone hydrochloride sublingual spraying drug delivery system or composition and its preparation method	CN	Animal PK data only
	19.09.2007	101036650	Xue Jing	Naloxone hydrochloride dropping pills	CN	No PK data
	19.09.2007	101036651	Xue Jing	Naloxone hydrochloride spraying agent for mouth and nose	CN	No PK data
2006	01.02.2006	1726915	PLA Academy of Military Science	Nasal cavity taken drug system and combination of naloxone hydrochloride and preparation method	CN	Animal PK data only
2005	09.02.2005	1575795	PLA Academy of Military Science	Naloxone hydrochloride nasal spray	CN	No PK data
	19.01.2005	1565451	PLA Academy of Military Science	Naloxone Hydrochloride nose powder preparation	CN	No PK data
2004	08.02.2004	132646	Pentech Pharmaceuticals, Inc.	Controlled release of drugs delivered by sublingual or buccal administration	IL	No PK data
2000	26.10.2000	WO/2000/062757	Britannia Pharmaceuticals	Composition containing opioid antagonists and spray dispenser	WO	No PK data
	07.06.2000	2349818	Britannia Pharmaceuticals	Spray dispenser for opioid antagonists	GB	No PK data
1997	20.08.1997	790058	Inresa Arzneimittel	Therapeutic use of transdermal naloxone (naloxone TTS)	EP	No PK data
1996	01.05.1996	0709088	Labtec	Transdermal therapeutic system for application of naloxone	EP	No PK data
	11.01.1996	4423850	Labtec	Transdermal delivery device for naloxone hydrochloride	DE	No PK data
1989	06.06.1989	1255229	ALZA Corporation	Transdermal therapeutic systems for the administration of naloxone, naltrexone and nalbuphine	CA	No PK data
1986	04.03.1986	4573995	ALZA Corporation	Transdermal therapeutic systems for the administration of naloxone, naltrexone and nalbuphine	US	No PK data
1985	12.03.1985	1183778	University of Kentucky Research Foundation	Method of administering narcotic antagonists and analgesics and novel dosage forms containing same	CA	No PK data
1984	07.08.1984	4464378	University of Kentucky Research Foundation	Method of administering narcotic antagonists and analgesics and novel dosage forms containing same	US	Animal PK data only
1984	11.11.1982	WO/1982/003768	University of Kentucky Research Foundation	Novel method of administering narcotic antagonists and analgesics and novel dosage forms containing the same	WO	Animal PK data only

Annotations: CA: Canada; CN: China; DE: Germany; EP: European Parliament; Exclusion: reason for exclusion; GB: Great Britain; IL: Israel; RU: Russia; SG: Singapore; US: United States; WO: World Intellectual Property Organization (WIPO), ZA: South Africa.

Chapter 7 Early Study of Concentrated Nasal Naloxone

Preface

In this chapter I report on data from a Phase-I pharmacokinetic study in healthy volunteers originally conducted in 2004.

In late 2014, the Cambridge-based pharmaceutical company Mundipharma Research Limited began consulting with my first supervisor regarding the potential development of a naloxone nasal spray for overdose reversal (see Chapter 8). Ten years prior, Purdue Pharma L.P., the U.S.-based partner company of Mundipharma, had developed and tested two concentrated nasal naloxone formulations as part of a study that aimed to explore the abuse liability of an opioid analgesic formulation. In 2012, Euro-Celtique S.A., an independent associated company of Mundipharma Research Limited, then patented these formulations (WO/2012/156317), as already described in Chapter 6.

In discussion with my first supervisor, Mundipharma shared Excel graphs from the 2004 Purdue study. These graphs appeared to depict only the mean naloxone absorption profiles for the nasal spray formulations tested, as already reported in the Euro-Celtique patent. However, a serendipitous discovery led to the realization that the original dataset from the 2004 trial was indeed embedded in the Excel graphs. I was subsequently granted permission from Mundipharma to conduct a new analysis of the original dataset from the 2004 trial, with focus on early naloxone absorption and potential of the nasal spray formulations for opioid overdose reversal.

My analysis, as described in this chapter, has also been published as a first-authored short report entitled “Pharmacokinetics of concentrated naloxone nasal spray over first 30 minutes post-dosing: analysis of suitability for opioid overdose reversal” in the journal *Addiction* (Mundin, McDonald, et al., 2017).

The results show that concentrated naloxone nasal spray has a promising pharmacokinetic profile, with substantial bioavailability and early absorption. Moreover, the concentrated naloxone spray does not appear to cause nasal mucosa irritation or other adverse events related to the intranasal route of administration. Building on these results, Mundipharma conducted a larger Phase I trial of different nasal naloxone formulations in 2016, with the explicit aim of testing nasal naloxone formulations for overdose reversal. This more recent study is the subject of Chapter 8.

7.1 Introduction

Some opioid overdoses have insidious onset, while others occur rapidly. Darke and Duflou (2016) recently analyzed the time course of opiate metabolites post-mortem and concluded that heroin overdose death occurred within 20-30 minutes of injecting in 43% of cases, suggesting the time window for naloxone administration may be very narrow (Tas & McDonald, 2016). Hence, analysis of naloxone pharmacokinetics in the first 20-30 minutes is vital.

This chapter focuses on early naloxone exposure and presents a new analysis of previously unpublished data from a 2004 pharmacokinetic study of naloxone nasal spray. The 2004 study had originally been conducted by Purdue Pharma LP (US) for another reason, namely to investigate abuse liability of an oral oxycodone/naloxone formulation. This chapter re-examines the retrieved data in order to consider the potential of the tested high-concentration intranasal (IN) naloxone formulations from the different perspective of overdose reversal, with two aims:

- Aim 1: to describe the pharmacokinetic properties of two high-concentration IN naloxone formulations
- Aim 2: to assess naloxone absorption in the clinically-relevant period of the first 30 minutes post-administration.
- Aim 3: to assess dose proportionality of the two IN naloxone formulations.

7.2 Methods

This section describes the original study design and procedures, and the subject selection, and then also reports the new analyses conducted to investigate the study aims.

7.2.1 Study design

Participants had received naloxone in four dose/route combinations (one per session) in an open-label, randomized, 4-way crossover Latin-square design in the original study. A crossover design designates a type of longitudinal study in which subjects are randomly allocated to a series of different treatments on different occasions. Since crossover designs allow for within-subject comparisons, a washout period between all treatment sessions is needed to minimize the risk of carryover effects, i.e. treatment residue from one session remaining present in the following session. In pharmacokinetic studies in

human subjects, the minimum wash-out period is typically three days, and its duration is determined by the half-life of the active ingredient (including metabolites) to be tested. Relative to between-subject designs, crossover designs need a fewer number of subjects to produce meaningful results (Kar, 2011; p. 263). This makes the design particularly well-suited for the first-in-human study of new drug formulations, where smaller sample sizes are preferable to minimize human subject exposure to potentially unknown side effects of a drug. The Latin square is a special case of crossover designs that aims to reduce the experimental error by counterbalancing the distribution of the two potential error sources (variability in treatment sessions, subjects) so that the treatment effect of interest can be tested more sensitively (MacKenzie, 2013).

1	2	3	4
2	1	4	3
3	4	1	2
4	3	2	1

Figure 23 Latin square design[17]

The study had involved four dosing sessions which compared naloxone plasma concentrations from single-dose treatments, with a minimum 14-day washout between treatment sessions. The study duration was 45 days per subject, plus screening. Study subjects were healthy volunteers and received the following four treatments:

- **A:** 1mg/mL intravenous (IV) reference (into the fossa ante cubital)
- **B:** 16mg/mL sublingual (SL) administration (from 16mg/mL solution)
- **C:** 8mg/0.4mL IN administration (from 20mg/mL solution)
- **D:** 16mg/0.4mL IN administration (from 40mg/mL solution).

The rows and columns of the square illustrated in Figure 23 represent the levels of the two extraneous factors (sessions, subjects). The Arabic numerals designate the four

[17] Source: https://plus.maths.org/issue38/features/aiden/table9.gif

naloxone treatments, with each treatment occurring only once per position of the treatment sequence and only once per subject.

7.2.2 Study procedures

Data collection had originally been conducted between May 3 and June 27, 2004 at the Clinical Pharmacology Unit at Ohio State University (Columbus, OH, USA).

Naloxone hydrochloride 10mg/10mL vials had been obtained from Bristol-Meyers Squibb (USA), and intravenous naloxone hydrochloride injection was administered as a 1mg/mL bolus.

Sublingual solution (16mg/mL) had been prepared by the site pharmacy by dissolving naloxone hydrochloride powder (Mallinckrodt Pharmaceuticals, USA) in 0.9% sodium-chloride solution per study instructions. For sublingual dosing, subjects were administered 16mg/mL solution which subjects were instructed to retain under the tongue for 5 minutes.

IN solution had been prepared by dissolving naloxone-hydrochloride powder (Mallinckrodt Pharmaceuticals, USA; 11.0g for 20mg/mL; 22.0g for 40mg/mL solution) in sodium-citrate stock solution (9.35g for 20mg/mL; 20.9g for 40mg/mL), and this solution brought up to 500mL volume using 0.9% sodium-chloride solution. IN solution was atomized using metered dose nasal spray devices (comprising a pump spray assembly threaded onto small amber glass bottle), with two 0.1mL aerosol actuations delivered per nostril, for a 0.2mL total volume per nostril. The droplet size of the nasal spray was not characterized.

Subjects were required to remain upright (seated or standing) with the head tilted slightly forward from dosing until 4 hours post-dosing.

7.2.3 Blood sampling and chemical analysis

Pharmacokinetic blood samples were drawn into tubes containing the anticoagulant K_2EDTA. Blood samples were collected pre-dosing, at minutes 1, 2, 4, 10, 30, 40, and at hours 1, 2, 4, 6, 8, 12, 16, and 24.

The original bioanalysis was conducted by Purdue Pharma L.P. (Ardsley, NY, USA). Naloxone plasma concentration was determined by a validated liquid extraction method using liquid chromatography-tandem mass spectrometry (LC-MS/MS; as described in Chapter 1). The range of quantification was 0.01-1.0 ng/mL for naloxone. (Subject

plasma samples were also assayed for the naloxone metabolite 6-alpha-naloxol, but 6-alpha-naloxol concentrations are not covered in this chapter, as the metabolite is not considered clinically meaningful (Schulteis, 2009). Naloxone concentrations below the limit of quantification were set to zero for pharmacokinetic calculations.

7.2.4 Pharmacokinetic analysis: Outcome measures for this new analysis

The pharmacokinetic analysis program Phoenix WinNonlin 6.4 (Certara; Princeton, NJ, USA) was used to derive standard pharmacokinetic parameters from blood plasma naloxone concentrations at the above sampling time points using non-compartmental analysis. Non-compartmental analysis is a standard technique for the assessment of pharmacokinetic data and represents a simple alternative to model fitting by nonlinear regression analysis (Gabrielsson & Weiner, 2012). Non-compartmental pharmacokinetic analysis is not dependent on compartmental models, i.e. hypothetical structures used to describe how a drug is processed in a biological system following dosing. Instead, non-compartmental analysis is based on the estimation of drug exposure, i.e. area under the curve (AUC). Since it involves fewer model assumptions, non-compartmental analysis is considered the method of choice for studies that aim to determine the degree of exposure from a drug (e.g. naloxone) and its associated pharmacokinetic parameters (Gabrielsson & Weiner, 2012). Non-compartmental analysis estimates AUC using the trapezoidal rule. The trapezoidal rule treats each segment of the plasma concentration-time curve as a trapezoid, i.e. a four-sided figure where the adjacent sampling time points along the x-axis are the two parallel sides (Bourne, 2016). The trapezoidal rule is thus a numerical approximation method which allows us to calculate AUC directly from the concentration versus time data. The AUC of each individual segment can be determined by multiplying the segment width by the average plasma concentration (Cp; see Figure 24). For the segment from time points (t) 2 to 3, the segment width is determined by the distance between the two sampling time points:

$$AUC_{2-3} = \frac{Cp_2 + Cp_3}{2} \bullet (t_3 - t_2)$$

Figure 24 Formula for AUC of an individual segment in trapezoidal method[18]

[18] Source: https://www.boomer.org/c/p4/c02/c0208.html

Analogous to numerical integration, the total AUC can then be determined by addition of the individual segments (see Figure 25).

$$AUC_{1-n} = \sum \left\{ \frac{Cp_1 + Cp_2}{2} \bullet (t_2 - t_1) \right\} + \left\{ \frac{Cp_2 + Cp_3}{2} \bullet (t_3 - t_2) \right\} + \dots$$

Figure 25 Formula for AUC of multiple segments in trapezoidal method[19]

Due to the dependence on the segment width, i.e. the duration of the blood sampling interval, the accuracy of the AUC is higher the more frequent blood sampling occurs, i.e. when the trapezoids are more likely to represent the actual shape of the plasma naloxone concentration-time curve.

Non-compartmental analysis does not assume that the plasma naloxone concentration is identical to naloxone concentration at the target site (e.g. opioid receptors in the brain). Rather, any changes in the plasma naloxone concentration are assumed to quantitatively reflect changes in naloxone availability at the target site (see also Chapter 1) (Dhillon & Gill, 2006).

The potential of IN naloxone for opioid overdose reversal was of main clinical interest for this new analysis, and consequently I focused on analysis of the pharmacokinetics within the first half-hour, examining plasma naloxone sample concentrations from dosing to 30 minutes.

Partial AUC values were determined from dosing to 1, 2, 4, 10, and 30 minutes. AUC values are expressed as h*ng/mL, i.e. hour(s) times nanograms per milliliter, representing naloxone exposure over time.

The exploratory parameter T50%, defined as time from dosing to concentration equal to 50% of maximum naloxone plasma concentration (Cmax) (Strang, McDonald, Tas, & Day, 2016) (see also Chapter 4), was introduced as additional measure of early absorption.

[19] Source: https://www.boomer.org/c/p4/c02/c0208.html

7.2.5 Statistical analysis

Inferential statistics were calculated using IBM SPSS Statistics 23 (Armonk, NY, USA). Analysis of variance (ANOVA) was conducted to determine if naloxone exposure from dosing up to 30 minutes (AUC30) was dose-proportional or if it differed by treatment arm. ANOVA is one of four standard approaches to test for dose proportionality (Deng, 2015). Following WHO guidance (Welink, 2009), dose-dependent AUC30 data were dose-adjusted (per mg; i.e. AUC30 values were divided values by dose) and log-transformed to allow for normal distribution in the ANOVA. Tukey's HSD test was used for post-hoc comparisons, with significance level at $p<.05$. The null hypothesis (H_0) assumes that dose-adjusted naloxone exposure up to 30 minutes (AUC30) post-dosing does not differ by IN formulation, i.e. $AUC30_{8mg}/8mg = AUC30_{16mg}/16mg$. Dose proportionality exists if the null hypothesis is not rejected, i.e. when there is no evidence against dose proportionality (Deng, 2015).

7.2.6 Protection of human subjects

Ethics approval had been sought and was granted by the Western Institutional Review Board (Olympia, WA, USA). The sponsor of the study (Purdue Pharma L.P., USA) did not register the study on the public clinical trials registry ClinicalTrials.gov. Since the study was conducted in 2004, i.e. prior to enactment of the US FDA Administration Amendments Act of 2007, registration was not required. Therefore, the study does not have a National Clinical Trial (NCT) identifier number. The study was performed in full compliance with Good Clinical Practice (GCP) regulations. Written informed consent was provided by each subject prior to commencement of any study-specific procedures. The enrolled study population was defined as any subject who signed an informed consent form.

7.2.7 Subject eligibility

Subjects were screened for eligibility within 14 days prior to the first dosing session. Eligible subjects were males and/or females aged between 18 and 55 years who were in good health as determined by no clinically significant findings in medical history and at screening, which comprised physical examination (including nasopharyngeal and oral cavity), electrocardiograms (ECGs), and clinical laboratory determinations. Planned enrollment was 12 subjects (i.e. equivalent to three 4x4 Latin Squares), which is within the FDA recommendation of 6-36 subjects (FDA, 1997).

7.2.8 Subject safety

Subjects' safety was assessed using adverse events, clinical laboratory results, vital signs, and ECGs. Subjects had an end-of-study medical evaluation after assessments for the fourth dosing were complete on day 45, or upon early study discontinuation. The safety population was defined as any subject who received any study treatment and had at least one subsequent safety assessment.

Table 21 Sample sizes by treatment

Subject ID	1mg IV	8mg IN	16mg IN	16mg SL
Subject 1	x	x	x	x
Subject 2	x	x	x	x
Subject 3	excluded as outlier	x	x	x
Subject 4	x	x	x	x
Subject 5	x	x	x	x
Subject 6	x	x	x	x
Subject 7	missing	x	x	missing
Subject 8	x	x	x	x
Subject 9	x	x	x	x
Subject 10	x	x	x	x
Subject 11	x	x	x	x
Subject 12	x	missing	x	x
Total	**n = 10**	**n = 11**	**n = 12**	**n = 11**

7.3 Results

7.3.1 Study participants and sensitivity analysis

Twelve eligible healthy subjects were entered into the study, which is within the FDA recommendation of 6-36 subjects (FDA, 1997); 5 were males (age 20-41 years, height 165-193cm, weight 74-106kg) and 7 females (19-48 years, 157-168cm, 51-83kg).

Subject 12 did not attend the final 8mg IN session, and Subject 7 failed to attend the 16mg sublingual and 1mg IV sessions. These three sessions were handled as missing data (see Table 21). The plasma naloxone concentration from Subject 3 was clearly anomalous at 20 minutes following IV administration, being 5-9 times greater than adjacent time points (10, 30 minutes) with an AUCt-value (26.85h*ng/mL) four times

greater than the group median (6.64h*ng/mL). Since original plasma samples are no longer available for chemical re-analysis, all IV data for this individual were excluded. Consequently, values reported below refer to sample sizes of n=10 (1mg IV), n=11 (8mg IN, 16mg sublingual), and n=12 (16mg IN), unless otherwise specified.

7.3.2 Pharmacokinetics

Plasma naloxone concentrations over the first 6 hours are displayed in Figure 26 (left-hand graph) and with expanded depiction of the first 30 minutes (right-hand graph). IV administration (1mg/mL) was characterized by rapid uptake and subsequent decline; whereas sublingual administration (16mg/mL) showed minimal absorption. Both IN administrations (8mg/0.4mL, 16mg/0.4mL) had similar time profiles, reaching peak concentrations in less than 30 minutes post-dosing. The 12 subjects' individual plasma-concentration curves are provided at the end of this chapter (see Figure 27, Figure 28, Figure 29).

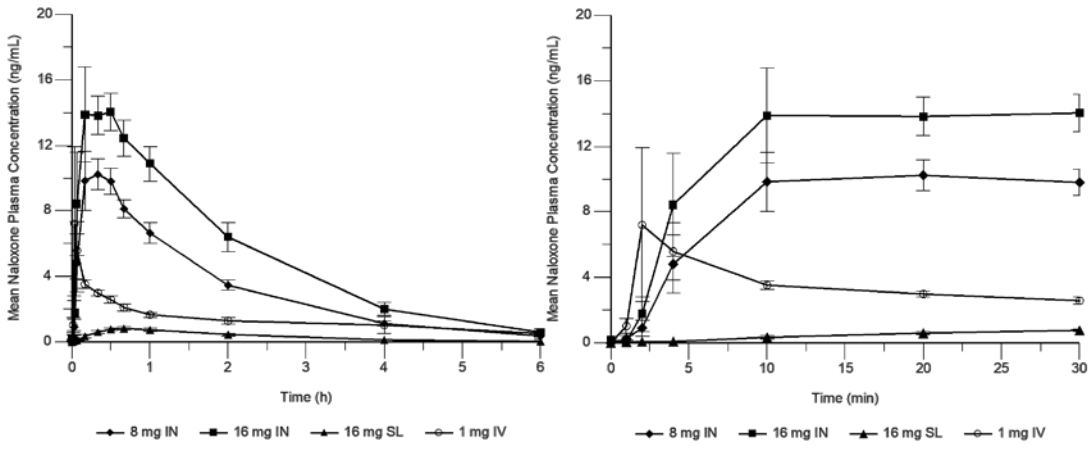

Figure 26 Mean naloxone plasma profiles within 6 hours (left) and expanded depiction of first 30 minutes (right) post-dosing (excl. Subject 3 IV outlier)

Table 22 Pharmacokinetic parameters (mean, SD)

Parameter	n	Unit	1mg IV	8mg IN	16mg IN	16mg SL
AUC20	10-12	h*ng/mL	1.24 (0.62)	2.50 (1.35)	3.58 (2.25)	0.11 (0.09)
AUC30	10-12	h*ng/mL	1.70 (0.62)	4.17 (1.68)	5.91 (0.30)	0.22 (0.11)
AUCINF	2-8	h*ng/mL	5.44 (0.60)	22.19 (4.39)	36.71 (10.60)	1.50 (0.42)
AUCt	10-12	h*ng/mL	8.83 (4.90)	20.07 (4.93)	32.81 (10.22)	2.67 (1.78)
Cmax	10-12	ng/mL	9.64 (12.66)	12.83 (4.47)	18.25 (7.50)	0.90 (0.37)
LambdaZ	2-8	1/h	0.75 (0.02)	0.07 (0.04)	0.06 (0.03)	0.64 (0.14)
t1/2Z	2-8	h	0.93 (0.02)	14.84 (13.21)	16.60 (15.08)	1.12 (0.22)
T50%	10-12	h	0.06 (0.05)	0.12 (0.06)	0.13 (0.07)	0.24 (0.10)
Tmax^	10-12	h	0.07 (0.03, 4.00)	0.33 (0.07, 0.50)	0.33 (0.07, 0.67)	0.67 (0.50, 36.00)

Annotations: AUC20 = partial area under the curve (AUC) from dosing to 20 minutes; AUC30 = partial AUC from dosing to 30 minutes; AUCINF = AUC from dosing up to infinity; AUCt = AUC from dosing to last measurable time point; Cmax = maximum observed plasma concentration; Tmax = time to Cmax; ^median (min, max). LambdaZ = terminal phase rate constant; t1/2Z = terminal phase half-life

Pharmacokinetic parameters are shown in Table 22. The two IN administrations (8mg/0.4mL, 16mg/0.4mL) displayed similar uptake, with rapid median tmax of 20 minutes (0.33 h) for both doses. Mean T50% was 7-8 minutes for both IN doses (8mg IN: $\bar{x}$=0.12 h; 16mg IN: $\bar{x}$=0.13 h), and hence slower than from IV administration (4 minutes; $\bar{x}$=.06 h). Cmax values following 8mg IN ($\bar{x}$=12.83 ng/mL) and 16mg IN ($\bar{x}$=18.25 ng/mL) were greater than those following 1mg IV ($\bar{x}$=9.64 ng/mL). Cmax values following 16mg/mL sublingual naloxone were extremely low ($\bar{x}$=0.90 ng/mL).

Bioavailability

Dose-adjusted AUC data (per mg) from IN and SL administrations were compared against the 1mg IV reference. Bioavailability was determined using AUCt (area under the curve from dosing to last measurable time point) data rather than AUCINF (area under the curve from dosing up to infinity) data. Due to missing data in the terminal curves and resulting small sample sizes (n= 2-8), the AUCINF data were not considered reliable (see Table 22). Mean bioavailability estimates were determined for subjects for whom paired data (i.e. for the test treatment and the IV reference) were available. Since comparisons were not possible for missing and excluded sessions (see Table 21), absolute bioavailability was determined from AUCt data for sample sizes of n=9 (8mg IN) and n=10 (16mg IN, SL). The rationale for the sample sizes for the bioavailability comparisons is illustrated in Table 23.

Table 23 Sample sizes for bioavailability comparisons

Subject ID	8mg IN vs 1mg IV	16mg IN vs 1mg IV	16mg SL vs 1mg IV
Subject 1	x	x	x
Subject 2	x	x	x
Subject 3	Not available	Not available	Not available
Subject 4	x	x	x
Subject 5	x	x	x
Subject 6	x	x	x
Subject 7	Not available	Not available	Not available
Subject 8	x	x	x
Subject 9	x	x	x
Subject 10	x	x	x
Subject 11	x	x	x
Subject 12	Not available	x	x
Total	**n = 9**	**n = 10**	**n = 10**

The mean absolute bioavailability (F%) from dosing to last measureable concentration (AUCt) was 2.0% for sublingual naloxone; hence it was not considered further. IN administration had F% of 27.7% (8mg) and 24.6% (16mg; see Table 24).

Mean bioavailability values for partial AUC at 1, 2, 4, 10, 20, and 30 minutes post-dosing are also reported in Table 24, with similar increase over time for both IN doses (8mg, 16mg): >5% at 4 minutes, ≥13% at 10 minutes, ≥20% at 20 minutes.

Table 24 Absolute bioavailability (F%)

	AUC1	AUC2	AUC4	AUC10	AUC20	AUC30	AUCt
8mg IN	3.4%	2.4%	6.2%	17.5%	27.6%	33.1%	27.7%
16mg IN	1.2%	1.7%	5.0%	13.0%	19.5%	23.2%	24.6%

Annotations: F% values are based on partial AUCs (1-30 min. post-dosing) & AUCt

7.3.3 AUC30 and nasal dose equivalent to 1mg IV bolus

Observed AUC30 values following 8mg IN ($\bar{x}$=4.17 h*ng/mL) and 16mg IN ($\bar{x}$=5.91 h*ng/mL) were greater than following 1mg IV ($\bar{x}$=1.70 h*ng/mL; see Table 22) administration.

These AUC30 values were dose-adjusted, log-transformed and compared in a one-way, between-subjects ANOVA to test for dose-proportionality. AUC30 values differed significantly as a function of naloxone treatment [$F(3,40)=255.11$, $p<0.001$]. Post-hoc tests showed that dose-adjusted, log-transformed AUC30 was significantly higher with IV ($\bar{x}$=3.21, SD=0.15) versus both IN concentrations (8mg IN: $\bar{x}$=2.68, SD=0.19; 16mg IN: $\bar{x}$=2.53, SD=0.18). However, there was no significant difference between both IN concentrations ($p=0.230$), and the null hypothesis (H_0) was not rejected, confirming that naloxone absorption was proportional to IN dose administered.

Hence, with dose-adjusted AUC30 values for 8mg ($\bar{x}$=0.52 h*ng/mL per mg) and 16mg IN ($\bar{x}$=0.37 h*ng/mL per mg) and 1mg IV ($\bar{x}$=1.70 h*ng/mL) (from above observed values), one can calculate that, for AUC30, the IN-dose equivalent to 1mg IV would be 3.3mg IN (20mg/mL formulation) and 4.6mg IN (40mg/mL).

7.3.4 Safety

No serious adverse events occurred. Side effects reported after naloxone administration included fainting (3 cases; one each after 8mg IN, 16mg IN, 1mg IV), headache (2 cases) and gastrointestinal symptoms (5 cases). These 10 cases were distributed by treatment as follows: 8mg IN (3 cases); 16mg IN (5 cases); 16mg IN (0 cases); 1mg IV (2 cases).

7.4 Discussion

Recent WHO guidelines (WHO, 2014) recommend that, similar to adrenaline/epinephrine for the treatment of allergic shock (Hogue, Goss, Kelly Hollis, & White, 2016), naloxone should be offered to anyone in the community likely to suffer or witness an opioid overdose (‘take-home naloxone’, see Chapters 2 & 3). However, the lack of licensed non-injectable naloxone formulations until late 2015 (which continues outside North America) has impeded widespread THN implementation (Coffin & Sullivan, 2013a; Darke & Hall, 1997; Sporer & Kral, 2007; Strang et al., 2014; Strang et al., 1996).

Once non-injectable solutions exist, it is likely that naloxone can be provided more widely.

7.4.1 Statement of principal findings

The analysis reported in this chapter identifies a promising pharmacokinetic profile for concentrated naloxone nasal spray. In 2008, Dowling et al. reported only 4% absolute bioavailability with a nasal spray adaptation of a commercially-available concentration of naloxone (2mg/5mL), although the authors suggested the extremely low bioavailability may be a result of excessive volume at the nasal membrane. In sharp contrast, my analysis shows that, at much higher concentrations (8mg/0.4mL, 16mg/0.4mL), there is a mean absolute bioavailability between 25-28%.

My analysis also shows that, crucially, half of the maximum observed concentration (T50%) was reached within 8 minutes and maximum concentration (tmax) within 20 minutes of IN administration. This combination of bioavailability and time profile suggests that concentrated naloxone nasal spray may be suitable for the reversal of overdoses from heroin and other short-acting opioids (e.g. fentanyl), where rapid restoration of respiratory function within 30 minutes of opioid use may be essential (Darke & Duflou, 2016).

These results are broadly consistent with the recent paper by Krieter et al. (Krieter et al., 2016) who reported a Cmax of 10.3 ng/mL for a 8mg/0.2mL IN dose as well as tmax values of 18-30 minutes and bioavailability of 44-54% (relative to intramuscular reference) for 0.1-0.2mL of 20mg/mL and 40mg/mL IN formulations. (Among these, the 4mg/0.1mL formulation has been commercialized by Adapt Pharma under the trademarked name “NARCAN® Nasal Spray”

and approved for the North American market by the FDA (FDA, 2015) and Health Canada (CBCnews, 2016), see Chapter 4). However, absence of an intramuscular reference in the 2004 study by Purdue Pharma means that a direct bioavailability comparison between the studies is not possible.

7.4.2 Strengths and weaknesses of the chapter

This chapter reports on the first human PK data for concentrated nasal naloxone reported in the patent literature. My data analysis is novel in that it focuses on the clinically relevant first 30 minutes, and it also introduces the measure of T50%.

Several limitations need to be borne in mind. Some averages were based on low subject numbers (see Table 22). Particularly the terminal phase-dependent parameters AUCINF, LAMDAZ (terminal phase rate constant), and t1/2Z (terminal phase half-life) should be interpreted with great caution. Data were only available for 2-8 subjects (depending on naloxone treatment), and due to the long sampling period of up to 24 hours compared to the short half-life of naloxone (1±0.5 hours; see Chapter 1), the reported values for these parameters are likely unreliable. The accuracy of pharmacokinetic data obtained using non-compartmental analysis is negatively associated with the duration of blood sampling intervals. After the first hour post-dosing, the duration of the sampling intervals in the 2004 Purdue study ranged from 1-8 hours. Since the longer intervals were considered prone to measurement inaccuracies, the focus of this analysis was on AUCt (instead of AUCINF) and particularly on the clinically relevant first half hour post-dosing.

There was also variability in the tmax values for IV administration (median: 4 minutes), due to two outliers at 4 hours. The samples of these two outliers (Subjects 04 and 06) who had tmax values of 4 hours were not re-analyzed when the study was conducted in 2004. A discussion of the potential reasons for these outliers would thus be purely speculative.

It is also unclear if the low sublingual bioavailability resulted from subjects possibly swallowing (some of) the 1mL-volume of naloxone in saline, as the solution did not contain any additives to help keep it under the tongue.

For the nasal route, only a 0.2mL-volume per nostril was tested in this study, meaning that a volume-absorption relationship cannot be determined.

Finally, while it is generally assumed that atomization at a droplet size greater than 10µm increases nasal absorption (Kippax, Huck, Virden, Levoguer, & Suman, 2011), the droplet size distribution was not characterized in this study, and its potential impact on nasal deposition cannot be determined.

7.4.3 Possible mechanisms and implications for clinicians

The emergence of supportive pharmacokinetic data for concentrated IN naloxone, along with approval of a first nasal naloxone spray in North America (CBCnews, 2016; FDA, 2015), constitutes a significant advancement for the field, after concerns over off-label use of injectable naloxone-hydrochloride solution as nasal spray sparked a lively debate in early 2016 (Strang, McDonald, et al., 2016). My analysis shows that the early

absorption profile of concentrated nasal naloxone makes it suitable for emergency administration in the community, where rapid restoration of respiratory function is essential for opioid overdose reversal.

My analysis found no significant difference between the two nasal formulations in their dose-adjusted naloxone absorption (AUC30). As follows, it was possible to estimate an IN dose-equivalent that would deliver the same naloxone exposure within 30 minutes as the reference (1mg/mL IV bolus injection): A nasal dose of 3.3mg (at 20mg/mL) and 4.6mg (40mg/mL) would provide, over the clinically-critical initial 30-minute period, the same AUC30 as 1mg/mL IV. Based on these data, IN doses between 1.3mg and 3.7mg would equate to a 0.4–0.8mg parenteral dose range, as recommended by WHO (WHO, 2014).

As reported above, the concentrated intranasal naloxone formulations had a good safety profile in healthy volunteers. The incidence of all treatment-related adverse events was similar across all four treatment groups and thus neither specific to intranasal administration nor proportional to intranasal naloxone dose. No symptoms of nasal mucosa irritation were reported in the safety assessment. These observations are encouraging for the use of concentrated naloxone spray formulations in clinical practice.

7.4.4 Possible mechanisms and implications for policymakers

The time-lag between the original study conducted thirteen years ago (with its results subsequently archived) and this new analysis warrants concern. The new analysis presented in the chapter identifies the potential of concentrated naloxone nasal spray for overdose reversal. There has recently been considerable public investment to conduct healthy volunteer studies of nasal naloxone (Krieter et al., 2016). The field could have progressed faster if there had been awareness of the above data. In future, policymakers should put a mechanism in place to ensure awareness of relevant data by industry and academia.

7.4.5 Questions for future research

While the above findings support good bioavailability of 20mg/mL and 40mg/mL IN formulations in healthy subjects, the 8mg and 16mg IN doses were originally studied for different reasons. The pharmacokinetics of doses appropriate for OD reversal have yet to be tested in healthy volunteers (see Chapter 8).

Moreover, concentrated naloxone nasal spray has yet to be formally tested in the target population of opioid users. Algorithms exist for injectable naloxone to guide correct initial and repeat dosing (Clarke, Dargan, & Jones, 2005) but have yet to be developed for IN naloxone. The T50% data suggest that initial IN absorption is delayed compared to the IV bolus, with IN administration taking 7-8 minutes to attain half of the peak concentration (versus 4 minutes for IV), and IN absolute bioavailability only surpassing 10% between 4-10 minutes (see Table 22). If this finding is robust, then lay responders may need to be advised to wait some minutes before administering a second IN dose to avoid risk of precipitating over-antagonism. Dose-titration protocols and repeat-dosing guidance for IN naloxone will need development, especially for take-home distribution to drug users, peers, and family members without medical training.

7.5 Conclusion

Concentrated naloxone nasal spray appears to be a feasible formulation with adequate speed of onset and acceptable bioavailability in the concentrated form. This appears directly relevant to prevention of opioid overdoses in medical settings and in the community (take-home naloxone). The above data find high doses of concentrated nasal spray solutions (8mg and 16mg from 20mg/mL and 40mg/mL, respectively) to have acceptable bioavailability and plasma levels over the clinically-critical first 30 minutes, with moderate uptake from 4-10 minutes onwards. Based on the naloxone plasma concentrations obtained from 8mg and 16mg IN naloxone administration, it was possible to estimate what IN doses would lead to similar naloxone exposure as a 0.4-0.8mg parenteral injection. Chapter 8 covers the study and identification of such lower IN doses appropriate for use in clinical practice.

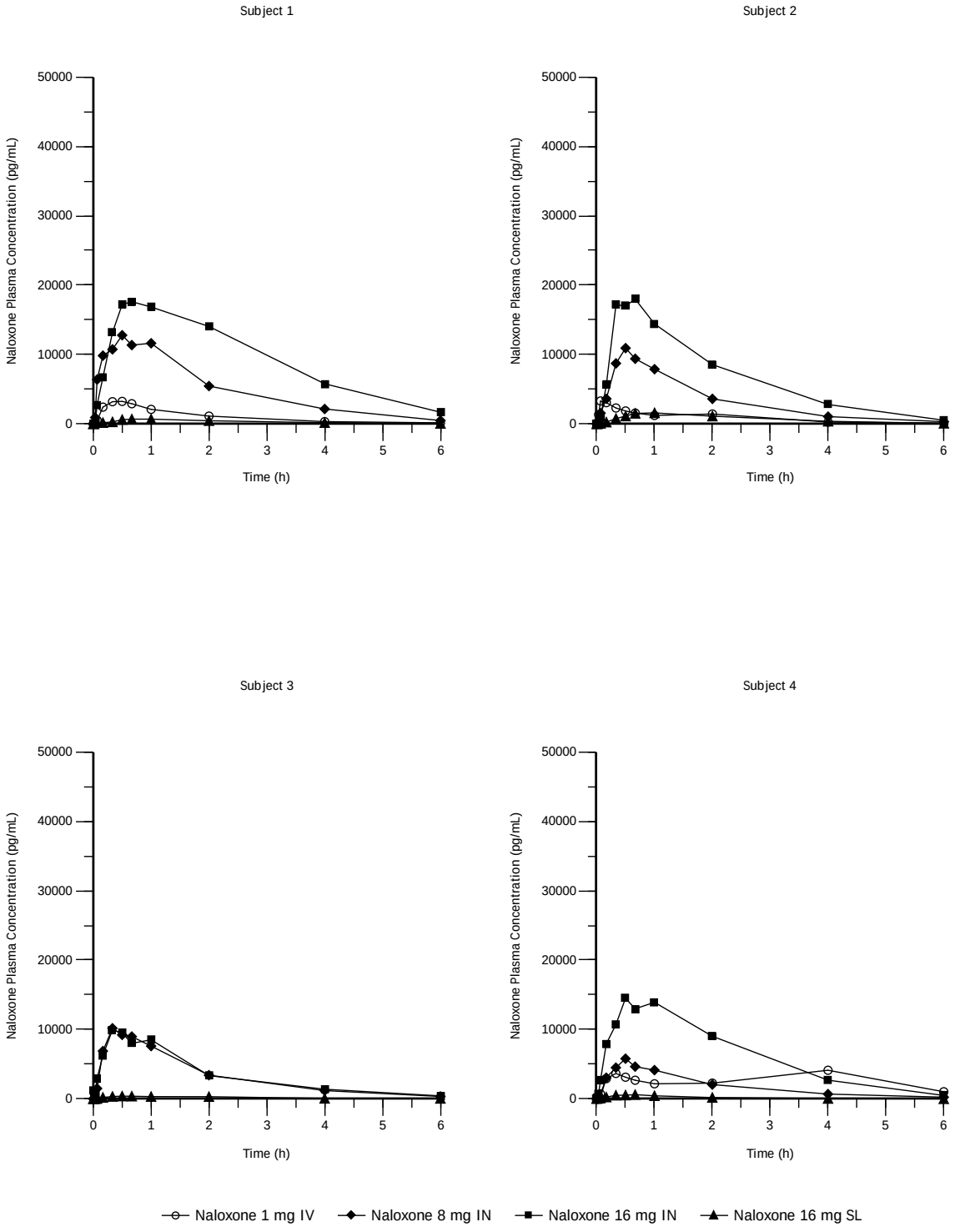

Figure 27 Subjects 1-4: Individual naloxone plasma profiles within 6 hours post-dosing (excl. Subject 3 IV outlier; N.B. concentrations are provided as pg/mL)

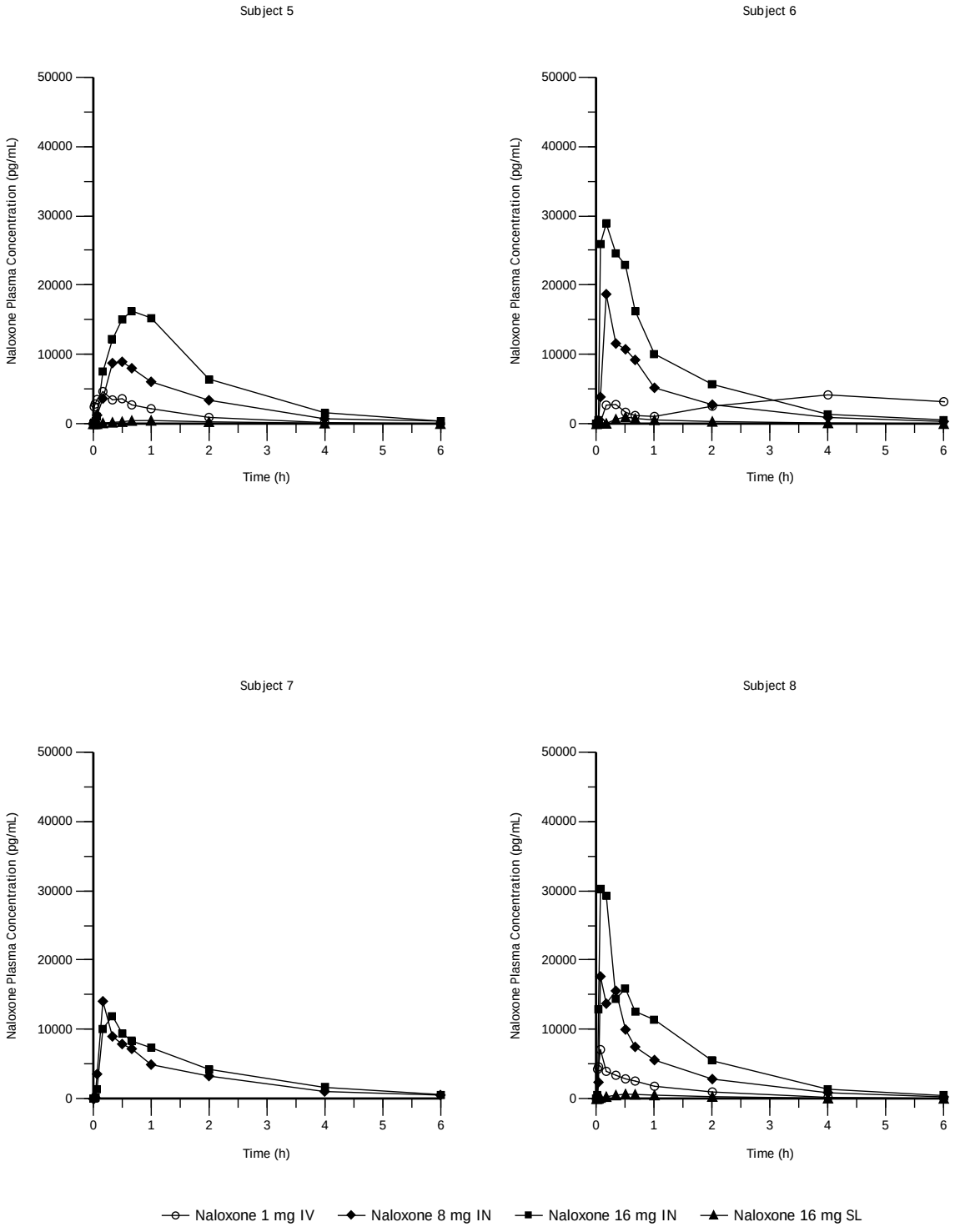

Figure 28 Subjects 5-8: Individual naloxone plasma profiles within 6 hours post-dosing (N.B. concentrations are provided as pg/mL)

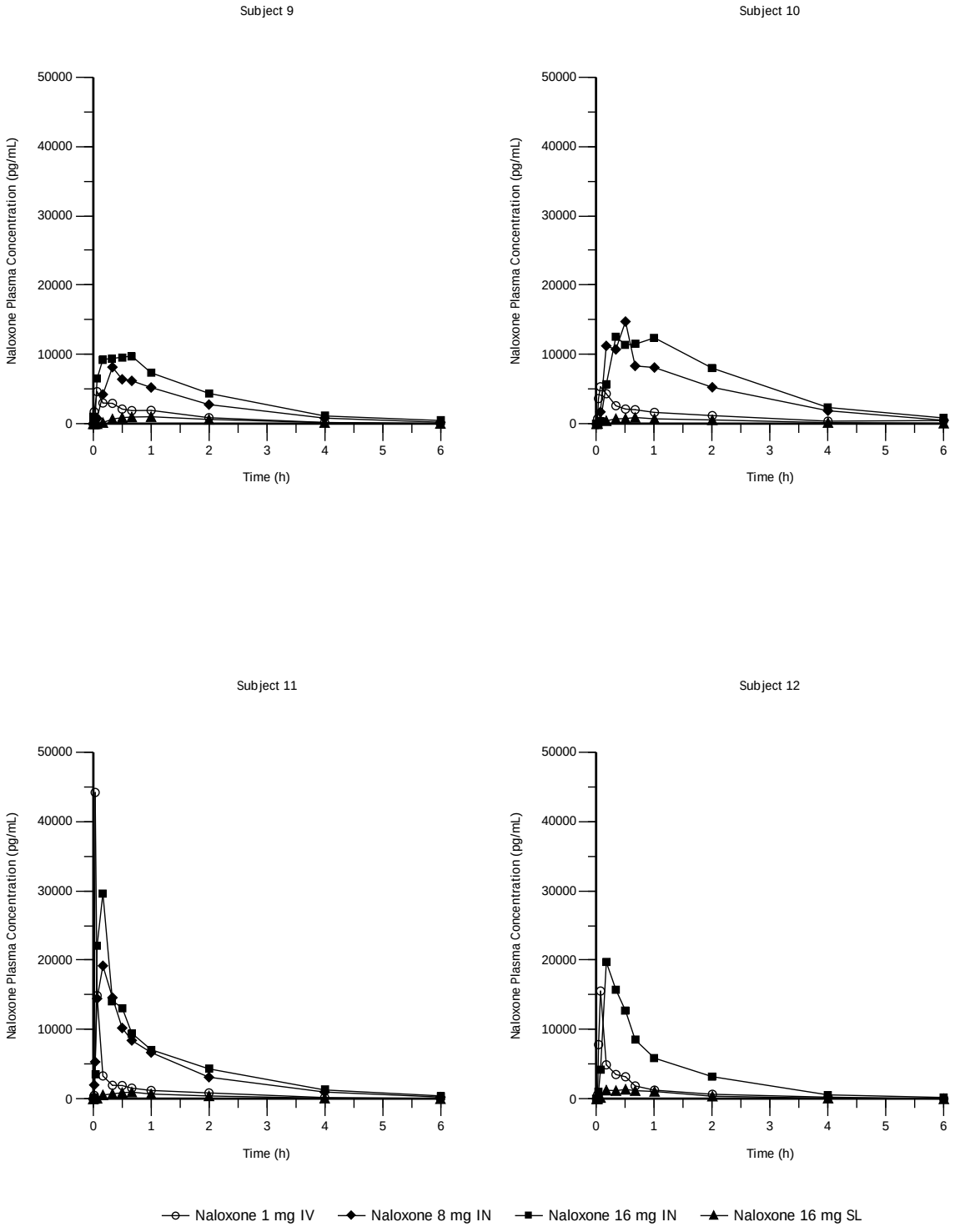

Figure 29 Subjects 9-12: Individual naloxone plasma profiles within 6 hours post-dosing (N.B. concentrations are provided as pg/mL)

Chapter 8 New Study of Concentrated Nasal Naloxone

Preface

In this final chapter on nasal naloxone, I present my data analysis of a 2016 UK-based Phase-I pharmacokinetic study of two intranasal naloxone formulations developed specifically for opioid overdose reversal. Between October and December 2016, I had the opportunity to undertake an unpaid student industry placement with Mundipharma Research Limited in Cambridge. My role was to conduct the data analysis of the Phase-I naloxone trial, both in collaboration with Mundipharma staff and also independently, and to interpret the data with regard to their clinical significance. I was also involved in the preparation of the regulatory submission to the European Medicines Agency. In late 2015, my supervisor and I had advised Mundipharma on the research design for this Phase-I trial. Among others, this is reflected in the blood sampling time points, which were adapted from the clinical trial protocol that I had devised to test a novel buccal naloxone tablet, see Chapter 9. This sampling time series would allow for precise study of early naloxone blood concentrations as well as for future comparison with the concentrations obtained for the buccal tablet. Sponsored by Mundipharma, trial recruitment and data collection were outsourced to Richmond Pharmacology and took place between March and April 2016. I observed naloxone dosing and blood sampling during the last-patient-last-visit session on April 27, 2016. While Chapter 7 has already covered the pharmacokinetics of concentrated naloxone nasal spray (n=12) with focus on early absorption, this recent Phase-I trial is stronger in design. It includes an intramuscular reference (as per FDA guidelines, see Chapter 5) in addition to the intravenous reference, the sample size was considerably increased to n=38 (from n=12), and the intranasal doses were adjusted to reflect potential use in future clinical practice. I presented the results of this chapter at the SSA Annual Symposium 2016 and have been invited to give an oral presentation of these results at the CPDD (College on Problems of Drug Dependence) 79th Annual Meeting in Montreal, Canada in June 2017. I submitted a first-authored research report ("Pharmacokinetics of concentrated naloxone nasal spray for opioid overdose reversal: Phase-I healthy volunteer study") to Addiction on April 30, and the manuscript is currently under review.

The data in this chapter may in the near future form the basis of a new licensed naloxone nasal spray in Europe – subject, of course, to the decisions from relevant regulatory authorities.

8.1 Introduction

For nasal naloxone spray to be effective, the dose must be adequate but not excessive, and early absorption must be comparable to intramuscular (IM) injection (see description of FDA criteria in Chapter 5). My re-analysis of a historical dataset in Chapter 7 provided proof-of-concept for substantial naloxone exposure from administration of concentrated nasal spray. However, the original study was conducted in 2004 for a clinical indication different from opioid overdose reversal, and the intranasal (IN) doses tested (8mg, 16mg) were far in excess of the FDA-recommended parenteral reference dose of 0.4mg naloxone.

Since June 2016, two studies have been published which report on the pharmacokinetics of different IN naloxone formulations developed for opioid overdose reversal: a US analysis by Krieter et al. of the FDA and Health Canada-approved 4mg/0.1mL nasal spray (NARCAN®) (Adapt, 2015; FDA, 2015; Krieter et al., 2016) (CBCnews, 2016) (see Chapter 4) and, more recently, a Norwegian study by Tylleskar et al. (2017) of a 8mg/mL formulation.

Results from these two recent studies and the 2004 PK study in Chapter 7 conflict with a 2008 report by Dowling et al. (2008): It seems likely that it is the highly-concentrated naloxone formulations which explain the better IN bioavailability of 46-54% (4mg/0.1mL relative to IM) (Krieter et al., 2016), 52-54% (0.8/0.1mL and 1.6mg/0.2mL dose relative to intravenous (IV)) (Tylleskar et al., 2017), and 25-28% (8mg/0.4mL and 16mg/0.4mL relative to IV) (Mundin, McDonald, Smith, Harris, & Strang, 2017) (see Chapter 7), in contrast to the extremely low bioavailability (4%, relative to IV) reported by Dowling et al. (2008) for a 2mg/5mL formulation.

In the UK, through a recent collaboration between the Cambridge-based pharmaceutical company Mundipharma Research Limited and the Addictions Department at King's College London, my supervisor and I have explored different concentrated IN formulations. The objective was to develop a nasal spray suitable for lay administration, which would produce rapid onset of action and adequate exposure during the overdose crisis, without risk of 'over-antagonism' (Hertz, 2012; Neale & Strang, 2015; UKMi, 2016). A PK study in healthy volunteers was conducted in early 2016 with the aim to identify an IN dose that would provide, during the crucial initial minutes following administration, a comparable naloxone plasma level and bioavailability to that provided by IM naloxone injection. In this chapter, I report on the PK characteristics of two purpose-made nasal naloxone formulations (10mg/mL, 20mg/mL) administered at three different doses, with focus on early absorption.

The primary aims of this chapter are to twofold:

- Aim 1: To assess the PK profile of IN naloxone
- Aim 2: To compare its early partial systemic exposure to the IM reference.

The secondary aim was as follows:

- Aim 3: To determine IN bioavailability.

8.2 Methods

8.2.1 Study design

A randomized, open-label, 5-way cross-over study (EudraCT number: 2015-004493-15) was conducted to determine naloxone pharmacokinetics from highly-concentrated nasal spray solution (10mg/mL, 20mg/mL; Summit Biosciences, US) at three doses.

IN naloxone was administered as atomized spray with the Unit Dose System (Aptar Pharma, US). As determined by laser diffraction for ≥94% of droplets, the droplet size was greater than 10µm to ensure deposition of the spray in the nasal cavity.

The reference routes were IM (primary reference) and IV administration of proprietary naloxone hydrochloride solution (Braun Melsungen, Germany). The IM route with its recommended dose of 0.4mg naloxone served as primary reference, as it constitutes the clinical standard in out-of-hospital settings. The IV route of administration was included for assessment of absolute bioavailability.

Study subjects were healthy volunteers and received:

A. 1mg naloxone IN (1mg/0.1mL in one nostril)
B. 2mg naloxone IN (2mg/0.1mL in one nostril)
C. 4mg naloxone IN (2mg/0.1mL in each nostril)
D. 0.4mg naloxone IM (0.4mg/mL into the deltoid muscle of the shoulder)
E. 0.4mg naloxone IV (0.4mg/mL into the ante cubital fossa via a cannula)

The IN dose range was based on my analysis in Chapter 7 which identified 1-4mg IN as producing potentially similar early naloxone exposure as 0.4-0.8mg IV (Mundin, McDonald, et al., 2017), which is the injectable naloxone dose range recommended by WHO (2014). (The AUC data from dosing up until 30 minutes (AUC30) in Chapter 7 suggested that an IN dose between 3.3mg and 4.6mg would produce plasma naloxone levels equivalent to a 1mg IV injection). Over five study sessions, with sequence

randomly assigned in a cross-over design, each subject received all five study treatments, with a single naloxone dose per session. Each session was separated by at least a 4-day washout period. In each study session, subjects were confined to the study unit from check-in on the day before dosing until post-dose safety assessments were completed 24 hours after dosing. Dosing occurred in the fasting state. Subjects were in a fully supine position, remaining supine for at least 1-hour post-dose and thereafter semi-supine until at least 4-hours post-dose.

Vital signs (peripheral oxygen saturation (SpO_2), blood pressure, pulse rate, respiration rate, and body temperature) were monitored pre-dose (i.e. within an hour before dosing) and up to 24 hours post-dose. Adverse events (AEs) were recorded throughout the study. Subjects returned to the study unit for a post-study medical evaluation 4 days after the last dosing. The total duration of the study per subject was up to 42 days.

8.2.2 Blood sampling and chemical analysis

Given the special interest in early absorption, blood collection included high-frequency sampling over the first 15 minutes to capture early systemic exposure, with a total of 19 samples per session. Regular blood samples of 6mL each were taken pre-dose, at 1, 2, 4, 6, 8, 10, 12.5, 15, 30, 45 minutes and 1, 1.5, 2, 4, 6, 8, 10 and 12 hours after dosing. In total, approximately 570mL of bloods (19 samples of 6mL on 5 occasions) were taken per subject. Blood samples were centrifuged (1500g, 4^{o}C, 15 minutes) within 30 minutes of collection, with plasma stored (20^{o}C) within one hour. Naloxone plasma concentrations were quantified by LC-MS/MS methodology using a previously validated assay.

8.2.3 Pharmacokinetic analysis

Individual subject PK parameters for naloxone were derived using non-compartmental analysis in Phoenix WinNonlin 6.4 (Certara LP, US), a validated PK analysis program. The area under the concentration-time curve (AUCt) was determined using the trapezoidal method (see Chapter 7) from the time of dosing (0 h) to the final observed plasma concentration (Clast) for AUCt. The ratio of Clast to LambdaZ was used to estimate the area between the last measured time-point and infinity and added to AUCt to yield AUCINF. The maximum observed plasma concentration (Cmax) and the time to Cmax (Tmax) were obtained directly from plasma concentration data. LambdaZ was estimated using points in the terminal log-linear phase, and terminal phase half-life

(t1/2z) was determined from the ratio of the natural logarithm of 2 to LambdaZ. In addition to t1/2z, the half-value duration (HVD) was determined, which was defined as the time over which the plasma concentration for a given treatment remains above 50% of Cmax.

8.2.4 Bioavailability

Dose-adjusted AUC data (per mg) from IN administration were compared against the 0.4mg IM and 0.4mg IV reference doses. Mean bioavailability estimates were determined for subjects for whom paired data were available (see Chapter 7 for rationale).

8.2.5 Exploratory analyses

In addition to standard PK parameters, exploratory analyses were conducted to consider early exposure relative to the IM reference and repeat administration of naloxone treatments.

Early naloxone absorption

Based on previous observations that reliance on Tmax may not fully describe the early absorption curve (Strang, McDonald, et al., 2016), three exploratory PK parameters were introduced to assess early exposure from IN naloxone relative to the 0.4mg IM reference: T50%, AUCp, and, for IN administrations only, $T50\%_{REF}$. T50% was defined as the time taken to achieve blood levels of 50% of Cmax (see Chapter 4). AUCp designated the partial AUC from time of dosing to median Tmax of the reference treatment, i.e. the 0.4mg IM injection. The AUCp was thus equivalent to the AUC0-tmax interval, where tmax was the median tmax of the IM injection. $T50\%_{REF}$ was defined as the time taken to reach 50% of the Cmax of the primary reference (0.4mg IM).

Simulation of repeat administration:

Exploratory analyses involved simulation of repeat administration. In emergency medicine, naloxone doses may be repeated to achieve the necessary individualized dose (see Chapter 1) (BMJ, 2016; McEvoy, 2012). Therefore, simulations of repeat administrations were performed using the superposition approach. Superposition relies on linear pharmacokinetics and employs a simple overlay technique, assuming that the observed plasma concentrations after a single dose can be used to predict plasma

concentrations after multiple dosing (Gilbaldi & Perrier, 1982). The principle of superposition assumes that each dose acts independently, i.e. that absorption of one dose does not interact with absorption of a previous dose. This is illustrated in Table 25, where the plasma concentrations for the second dose and consecutive doses can be predicted for any time point by adding the concentration values in one row.

Table 25 Predicting plasma concentrations using superposition

Dose #	Time (h)	Dose 1	Dose 2	Dose 3	Concentration (∑ by row)
1	0	0	-	-	0
	1	59	-	-	59
	2	70	-	-	70
2	4	58	0	-	58
	5	50	59	-	109
	6	42	70	-	112
3	8	30	58	0	88
	9	25	50	59	134
	10	21	42	70	133
	12	15	30	58	103

Source: Modified from Gilbaldi & Perrier (1982)

Guidelines on the treatment of opioid overdose typically recommend initial administration of 0.4mg naloxone, repeated every 2-3 minutes if necessary (EMCDDA, 2016a; Hertz, 2012; UKMi, 2016; WHO, 2011b). Consequently, repeat administration of five doses of the 0.4mg IM reference was simulated at 3-minute intervals (simulating the upper limit of the recommended dose range, 2mg IM), versus two doses of 2mg IN at 3-minute intervals (simulating similar naloxone exposure, assuming 50% IN bioavailability).

Simulation of immediate administration of the full dose

Mindful of the crisis situation, non-medical first-responders may forget or ignore instructions and administer the full available dose. Therefore, the observed PK curves were also scales to doses of 5 x 0.4mg IM and 2 x 2mg IN, i.e. the total doses that would be available for a first responder to administer.

8.2.6 Protection of human subjects

The study was performed according to the Declaration of Helsinki (1964), International Conference on Harmonisation and Good Clinical Practice (CPMP/ICH/135/95) guidelines of the EMA and European Union Clinical Trials Directive 2001/20/EC. Approval was given by South Central – Berkshire B Research Ethics Committee (Reading, UK) in early March 2016. A copy of the ethics approval letter (REC reference: 16/SC/0033) is provided in Appendix A of this thesis. Written informed consent was provided by each subject.

8.2.7 Research site

Data collection was performed under supervision of Principal Investigator Dr. Ulrike Lorch (Richmond Pharmacology Ltd.) at the clinical trials facility Richmond Pharmacology Ltd. at Croydon University Hospital (UK), a non-NHS research site.

8.2.8 Subject eligibility

Volunteers (female and male) were eligible for participation if they were healthy and free of significant abnormal findings as determined by medical history, physical examination, vital signs, laboratory tests and ECG. Eligible volunteers had to be aged 18-55 years, body weight 55-100kg and BMI ≥18.5 and ≤30.0. Volunteers were excluded if they had abnormal nasal anatomy, nasal symptoms (e.g. polyps, blocked/runny nose), current or recent (within 7 days prior to screening visit) respiratory tract infections, or history of hay fever/seasonal allergy/rhinitis. Nasal passage examination was conducted at screening, pre- and immediately post-dose for IN treatment sessions. Volunteers were also excluded if they were recent smokers (within 90 days of first dosing session), or if they had positive results in the urine drug screen or alcohol test. Female volunteers were excluded if pregnant or lactating. Subjects attended a screening visit ≤ 21 days prior to the first dosing session and were enrolled into the study if they complied with these study entry criteria.

Table 26 Adverse events

System Organ Class	IN 1mg (N=33) n (%)	IN 2mg (N=36) n (%)	IN 4mg (N=34) n (%)	IM 0.4mg (N=32) n (%)	IV 0.4mg (N=34) n (%)	Total (N=38) n (%)
Subjects with at least one AE	3 (9.1)	7 (19.4)	3 (8.8)	2 (6.3)	7 (20.6)	17 (44.7)
GASTROINTESTINAL DISORDERS	**1 (3.0)**	**1 (2.8)**	**–**	**–**	**–**	**2 (5.3)**
Enamel Anomaly	–	1 (2.8)	–	–	–	1 (2.6)
Nausea	1 (3.0)	–	–	–	–	1 (2.6)
INFECTIONS AND INFESTATIONS	**1 (3.0)**	**2 (5.6)**	**1 (2.9)**	**–**	**3 (8.8)**	**7 (18.4)**
Gastroenteritis	–	–	–	–	1 (2.9)	1 (2.6)
Gingivitis	–	–	1 (2.9)	–	–	1 (2.6)
Nasopharyngitis	–	–	–	–	1 (2.9)	1 (2.6)
Oral Herpes	–	1 (2.8)	–	–	–	1 (2.6)
Rhinitis	–	–	–	–	1 (2.9)	1 (2.6)
Upper Respiratory Tract Infection	1 (3.0)	1 (2.8)	–	–	–	2 (5.3)
INVESTIGATIONS	**–**	**1 (2.8)**	**1 (2.9)**	**1 (3.1)**	**–**	**3 (7.9)**
Blood pressure decreased	–	1 (2.8)	–	1 (3.1)	–	2 (5.3)
Respiratory rate decreased	–	–	1 (2.9)	–	–	1 (2.6)
MUSCOLOSKELETAL AND CONNECTIVE TISSUE DISORDERS	**–**	**–**	**–**	**1 (3.1)**	**–**	**1 (2.6)**
Back pain	–	–	–	1 (3.1)	–	1 (2.6)
NERVOUS SYSTEM DISORDERS	**2 (6.1)**	**2 (5.6)**	**1 (2.9)**	**–**	**3 (8.8)**	**6 (15.8)**
Headache	2 (6.1)	2 (5.6)	1 (2.9)	–	3 (8.8)	6 (15.8)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**–**	**1 (2.8)**	**–**	**–**	**–**	**1 (2.6)**
Rhinitis Allergic	–	1 (2.8)	–	–	–	1 (2.6)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	**–**	**1 (2.8)**	**–**	**–**	**1 (2.9)**	**2 (5.3)**
Dermal Cyst	–	–	–	–	1 (2.9)	1 (2.6)
Nail Discolouration	–	1 (2.8)	–	–	–	1 (2.6)

AE: Adverse event. N: Number of subjects in Population. n: Number of subjects with data available. %: Percentage based on N. Note: A subject may have more than one AE in any category.

8.3 Results

8.3.1 Study participants

Thirty-eight eligible healthy subjects (age 20-54) were randomized, of whom 27 were males and 11 females. This sample size of n=38 is slightly above the recommended 6-36 subjects set out by FDA guidelines (FDA, 1997), as it was assumed that up to 20% of subjects might not provide valid PK data for the comparison of interest. In total, six subjects did not complete the study: six missed the 0.4mg IM session; five missed the 1mg IN session, four missed the 4mg IN and 0.4mg IV sessions, and two missed 2mg IN session. These 21 sessions were handled as missing data. Consequently, values reported below refer to sample sizes of n=32 (0.4mg IM), n=33 (1mg IN), n=34 (4mg IN, 0.4mg IV), and n=36 (2mg IN), unless otherwise specified.

8.3.2 Safety

No severe AEs occurred. In total, 17 (of n=38) subjects experienced 22 AEs (see Table 26), of which 11 AEs in 9 subjects were assessed as naloxone-related. AE-occurrence did not seem dose-related: 7 subjects experienced AEs after 2mg IN dose while only 3 subjects experienced AEs after 4mg IN dose.

8.3.3 Pharmacokinetic profiles

PK parameters are shown in Table 27. Mean plasma naloxone concentrations over the first two hours post-dosing are displayed in Figure 30 (left-hand graph), including expanded depiction of the first 20 minutes (right-hand graph).

IV administration (0.4mg) was characterized by an extremely rapid spike in plasma concentration, reaching early peak (mean Cmax 5.94ng/mL, median Tmax 2 minutes), followed by rapid decline over the next 10 minutes and gradual decline thereafter.

IM administration (0.4mg) was characterized by more gradual early uptake, leading to lower and later peak concentration (mean Cmax 1.27ng/mL, median Tmax 10 minutes), with flatter and slower decline thereafter. Overall exposure based on AUCt was comparable for IM and IV. The three IN doses tested (1mg, 2mg, 4mg) all achieved maximum plasma levels within 15-30 minutes (median Tmax). Mean Cmax values for 1mg IN (1.51ng/mL), 2mg IN (2.87ng/mL), and 4mg IN (6.02ng/mL) were greater than for IM.

Table 27: Pharmacokinetic parameters (mean, SD)

Parameter	Unit	1mg IN	2mg IN	4mg IN	0.4mg IM	0.4mg IV
AUCt *	h*ng/mL	2.56 (43.2)	4.86 (39.4)	10.01 (35.8)	2.01 (17.7)	2.01 (22.5)
AUCINF *	h*ng/mL	2.69 (40.5)	4.97 (38.5)	10.07 (35.8)	2.12 (16.6)	2.10 (21.1)
Cmax *	ng/mL	1.51 (50.2)	2.87 (49.6)	6.02 (54.5)	1.27 (55.8)	5.94 (92.9)
LambdaZ	1/h	0.55 (0.12)	0.53 (0.12)	0.44 (0.12)	0.53 (0.11)	0.57 (0.09)
t1/2Z	min	80 (23)	84 (30)	102 (28)	81 (16)	75 (13)
HVD	min	79 (40)	76 (33)	75 (38)	65 (67)	8 (12)
Tmax ^	min	15 (10, 60)	30 (8, 60)	15 (10, 60)	10 (4, 90)	2 (1, 15)

Annotations: AUCt = area under the curve (AUC) up to last measurable time point; AUCINF = AUC up to infinity; Cmax = maximum observed plasma concentration; LambdaZ = terminal phase rate constant; t1/2Z = terminal phase half-life; HVD = half-value duration; Tmax = time to Cmax; *geometric mean (CV%); ^median (min, max).

For all three IN doses, mean AUCt values (2.56-10.01 h*ng/mL) exceeded those of 0.4mg IM and IV (both: 2.01 h*ng/mL). Of the three IN doses, the 2mg dose most closely followed the 0.4mg IM curve during the first 10 minutes post-dose, reached blood levels at twice the 0.4mg IM dose by 15 minutes and maintained blood levels at more than twice the 0.4mg IM dose for the next two hours.

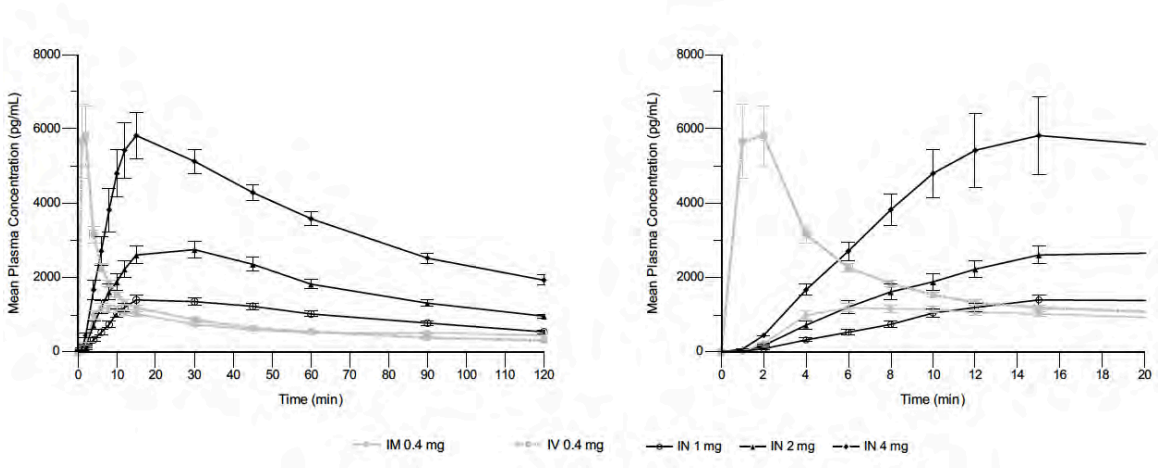

Figure 30 Mean plasma naloxone concentrations (observed values): dosing to 120 minutes (left) and dosing to 20 minutes (right)

8.3.4 Intranasal bioavailability

The mean absolute bioavailability (F%) estimates for IN naloxone (i.e. relative to IV) from dosing to last measureable concentration (AUCt) were 50.2% (1mg IN; n=32), 46.8% (2mg IN; n=33), and 48.1% (4mg IN; n=33), see Table 28. IN administration had a mean

bioavailability relative to IM (F_{IM}%) of 50.8% (from 1mg IN), 47.1% (2mg IN), and 48.3% (4mg IN), also determined from AUCt data (all n=32).

Table 28: Absolute (F%) and relative (F_{IM}%) mean bioavailability (90% CI)

	Reference	n	1mg IN	2mg IN	4mg IN
F_{IM}%	0.4mg IM	32	50.8 (45.2, 57.1)	47.1 (41.5, 53.5)	48.3 (43.2, 54.1)
F%	0.4mg IV	32-33	50.2 (44.6, 56.6)	46.8 (41.7, 52.6)	48.1 (43.3, 53.5)

Annotation: Bioavailability estimates are based on AUCt

8.3.5 Elimination

Following a single intranasal administration of the 1mg and the 2mg IN doses, the mean plasma half-life of naloxone was 80 minutes and 84 minutes, respectively. This differed only slightly from the 81-minute mean half-life observed for the 0.4mg IM reference. However, the 4mg IN dose (administered as two 2mg doses) exceeded the half-life of the IM reference by 21 minutes, with a mean value of 102 minutes. The half-value duration across all three IN doses (75-79 minutes) was substantially longer than for IM (65 minutes) and IV (8 minutes) administration, respectively.

8.3.6 Exploratory analyses:

Since the 2mg IN dose followed the 0.4mg IM reference most closely (see above), the 2mg IN dose was chosen as comparator against the IM reference in exploratory analyses.

Early naloxone absorption

Given the special interest in early uptake, I examined AUCp, T50%, and $T50\%_{REF}$ for the early part of the plasma concentration-time profiles for IN naloxone relative to the IM reference (see Table 29).

AUCp: The rounded partial AUC values, measured from dosing to Tmax of the IM reference, were equal for both 0.4mg IM and 2mg IN (mean: 0.11 h*ng/mL).

T50%: IM achieved plasma levels >50% of Cmax (C50%) at 4 minutes. The 2mg IN dose took 9 minutes to reach C50%.

$T50\%_{REF}$: The 2mg IN dose achieved concentrations equivalent to C50% of the IM reference at 6 minutes, i.e. within two minutes of the IM reference, suggesting IN and IM naloxone administration did not differ greatly in their early plasma concentrations.

Table 29: Exploratory pharmacokinetic parameters (mean, SD)

Parameter	Unit	1mg IN	2mg IN	4mg IN	0.4mg IM	0.4mg IV
AUCp *	h*ng/mL	0.05 (112.2)	0.11 (105.1)	0.27 (98.6)	0.11 (67.9)	0.44 (56.2)
T50%	min	10 (5)	9 (4)	9 (5)	4 (1)	1 (1)
$T50\%_{REF}$	min	10 (8)	6 (4)	4 (2)	(4 (1))	1 (2)

Annotations: AUCp = partial AUC with cut-off at Tmax of reference; T50% = time to 50% of Cmax; $T50\%_{REF}$ = time to C50% of 0.4mg IM (primary reference); *geometric mean (CV%).

Simulation of repeat administration

In the first simulation, the pharmacokinetics of repeated administration were explored. The bioavailability of IN naloxone (relative to IM, as reported above) was in the range of 47-51%, hence a 2:1 dose ratio (IN:IM) was assumed for the simulations, comparing cumulative 2 x 2mg IN doses at 3-minute intervals with five cumulative 0.4mg IM doses at 3-minute intervals (total 2mg IM). Figure 31 shows the peak plasma level from the observed 2mg IN dose occurring between those from the observed IM 0.4mg dose and the simulated 2mg IM dose (5 x 0.4mg administered 3 minutes apart). From this simulation it is evident that, in a hypothetical overdose scenario, a second dose of 2mg IN administered after 3 minutes (as broadly recommended for IM administration by the British National Formulary (BNF, 2017) would expose the patient to approximately the same naloxone levels, in terms of both initial rise in plasma concentrations and peak concentrations, as five consecutive IM 0.4mg doses (also 3 minutes apart), i.e. 2mg in total. In addition, the plasma naloxone levels from the simulated 2 x 2mg IN dose declined more slowly than the simulated 5 x 0.4mg IM administrations, indicating that plasma concentrations would be sustained for longer than those from IM dosing.

Simulation of immediate multiple dose administration of the full dose

In the second simulation (see Figure 32), the observed PK profiles, scaled in dose, were used to explore the pharmacokinetics of possible unintended immediate administration of the full 2mg IM injection (i.e. all five 0.4mg doses up to the top of approved therapeutic dose range) versus two simultaneous doses of 2mg IN. The scaled concentration data indicate that the 2mg IM dose would have fastest speed of uptake. In addition, the scaled

4mg profile (two 2mg IN doses) was compared with the observed data from the 4mg IN dose (administered as 2mg per nostril): the scaled 4mg IN profile lagged only slightly behind the observed 4mg IN profile. However, in terms of dose-adjusted AUC, the three administrations (2mg IM, 2x2mg IN, 4mg IN) were roughly equivalent.

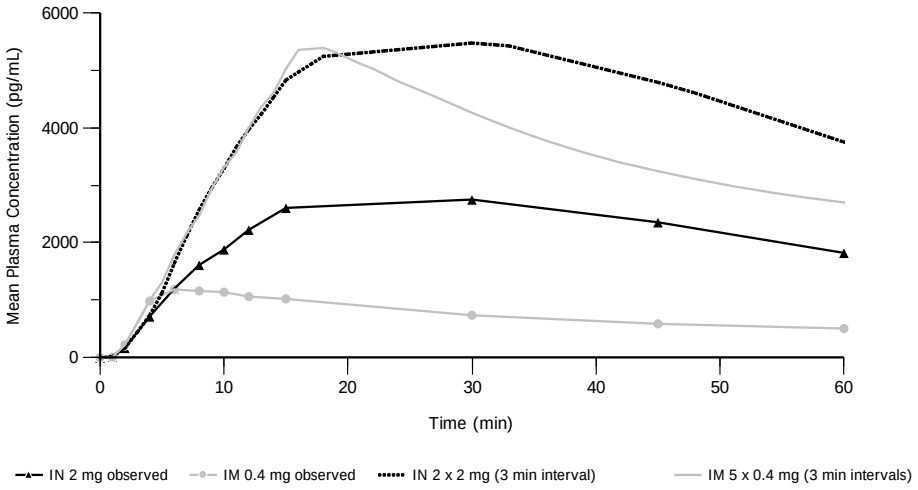

Figure 31 Scaled mean plasma naloxone concentrations after repeat administration at 3-minute intervals (vs mean observed profiles of 0.4mg IM and 2mg IN doses)

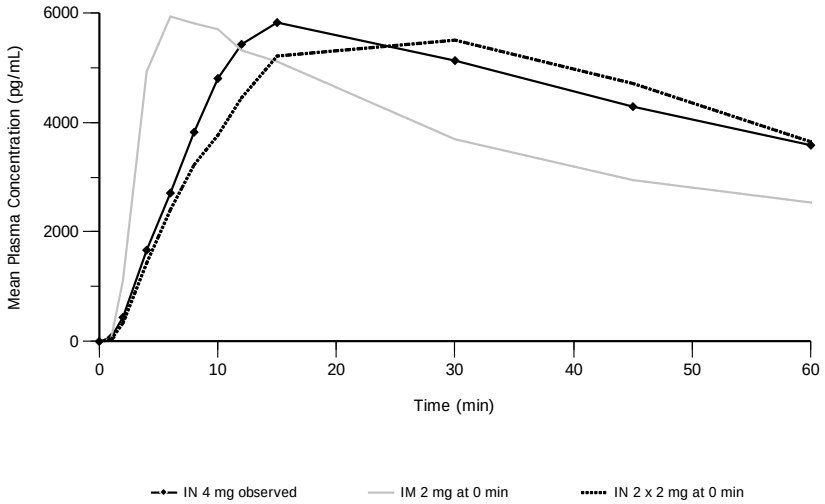

Figure 32 Scaled mean plasma naloxone concentrations after immediate administration of multiple doses at 0 minutes (vs mean observed profile of 4mg IN dose)

8.4 Discussion

8.4.1 Statement of principal findings

My analysis of the previously unpublished PK data in Chapter 7 established proof-of-concept for IN administration of concentrated naloxone formulations (Mundin, McDonald, et al., 2017). The results of this chapter suggest feasibility of concentrated naloxone spray at three doses (1mg/0.1mL; 2mg/0.1mL; 4mg as 2x2mg/0.1mL) for use by medical and non-medical first-responders.

Bioavailability

The results of this chapter confirm IN naloxone bioavailability of approximately 50% (both relative to IM and to IV), thus markedly different from the 4% absolute bioavailability reported for dilute IN naloxone formulation (2mg/5mL) by Dowling et al. (2008), yet very similar to the 52-54% absolute bioavailability reported by Tylleskar et al. (2017) and the 44-54% relative bioavailability reported by Krieter et al. (2016) for concentrated naloxone nasal spray formulations.

The importance of low volume for IN formulations, as already highlighted in Chapter 6, is also evident from comparison of the results from this chapter and those from the 2004 PK study covered in Chapter 7. In Chapter 7, I identified mean absolute bioavailability between 25-28% for two IN formulations (8mg/0.4mL, 16mg/0.4mL), i.e. only about half the absolute bioavailability (47-50%) of the data reported in this chapter. The 2004 PK study used a larger spray volume (0.4mL), which may have impacted absorption of naloxone from the nasal mucosa. From the results of the present chapter as well as Krieter et al. (2016) and Tylleskar et al. (2017), it appears that the administration of only 0.1mL volume of concentrated nasal spray likely reduces runoff and improves coating of the nasal mucosa and subsequent naloxone absorption.

Rapid absorption and slow elimination

With all three IN doses (1mg/0.1mL; 2mg/0.1mL; 4mg as 2x2mg/0.1mL) studied in this chapter, naloxone plasma concentrations increased rapidly, with median peak concentrations achieved between 15 and 30 minutes. These results are consistent with Tmax values of 18-90 minutes and 20-30 minutes reported for concentrated IN naloxone (also 0.1mL volume) by Tylleskar et al. (2017) and Krieter et al. (2016), respectively, and confirm that IN naloxone is rapidly absorbed into the systemic circulation via the nasal mucosa. In the study presented in this chapter, the 2mg/0.1mL IN dose resulted in early

uptake and exposure comparable to the 0.4mg IM reference, suggesting it may be a suitable alternative to an IM injection for community-based naloxone use.

It is interesting to consider the shape of the PK curves following IN naloxone administration. For all three IN doses, there is reasonably rapid early absorption, followed by good maintenance of plasma levels throughout the time period reported. This is in sharp contrast to the shape of the PK curves following IV (where the sudden rise in plasma level is followed by rapid decline) and IM administration (which mainly differs from the IV curve by lacking the initial spike). If IM is the reference route of administration, then, after dose-adjustment, concentrated nasal naloxone appears to offer comparable early onset followed by better maintenance of plasma levels over the intermediate period. The prolonged maintenance of naloxone plasma levels is reflected in the superior half-value duration of all three IN treatments (75-79 minutes) compared to the IM (67 minutes) and IV (12 minutes) reference treatments (see Table 27). With regard to the elimination pattern of nasally administered naloxone, it is also worth noting that the mean terminal half-life range reported by Krieter et al. (2016) (114-144 minutes) exceeded the values reported by Tylleskar et al. (2017) (70-90 minutes) as well as those observed for the three IN doses (80-102 minutes; see Table 27) in this chapter. It is unclear whether the variations in terminal half-life between the three studies may be due to differences in the excipients used in the IN naloxone formulations.

Inter-subject variability

It is also interesting to note that the inter-subject variability of IN naloxone exposure from dosing to AUCt was in the range of 36-43%, as demonstrated by the coefficient of variation (CV%). A lower degree of variation was seen with the IM (18%) and IV (23%) reference treatments. Variability was pronounced for early naloxone exposure from dosing to the Tmax of the IM reference (10 minutes; i.e. AUCp), with 99-112% for the three IN doses. Variability in AUCp values, though to a lesser extent, was also apparent for the IM (68%) and IV (56%) references. While a certain degree of variation is to be expected for non-injectable routes of administration, the inter-subject variability in AUCp data highlights that early naloxone exposure from the same naloxone dose may differ substantially among two subjects. The CV% values for the IN and injectable treatments indicate that there is unlikely a “one-size-fits-all” naloxone dose and that dose-titration may be required to reverse opioid overdose.

8.4.2 Strengths and weaknesses of the chapter

The central focus of my PhD project has been the study of non-injectable naloxone formulations to identify a dose and formulation comparable to IM administration (e.g. 0.4mg) that is also similarly appropriate for dose-titration, as currently recommended for the IM route (BNF, 2017). The exploratory dose simulations indicate that a 2mg IN dose provides opportunity for titration, with administration of a second 2mg IN dose resulting in similar naloxone exposure as a series of five IM 0.4mg doses (i.e. 2mg IM in total). Such an IN schedule would straddle the overall dose range of an "initial [injectable] dose between 0.4mg–2mg", as recommended by WHO (2014). The validity of the analyses presented in this chapter are strengthened by the intense sampling schedule during the clinically relevant first half-hour post-dosing (Darke & Duflou, 2016; McDonald & Tas, 2016): 9 samples were taken within this half hour, of which 6 samples in the first 10 minutes post-dosing alone. For comparison, the studies by Krieter et al. (2016) and Tylleskar et al. (2017) only comprised 6 to 7 post-dosing samples up to 30 minutes, with only 3 samples in the first 10 minutes post-dosing. This indicates that the AUCp data from dosing up to 10 minutes (i.e. tmax of the IM reference) was generated with greater accuracy in this study.

In addition, the study included both an IM and an IV reference (unlike Krieter et al. (2016) and Tylleskar et al. (2017) who only tested one injectable reference), allowing for better comparability of the bioavailability results across studies.

A weakness of the study concerns the fact that the Aptar devices were not weighed before and after dosing. Tylleskar et al. (2017) used 0.2mL Aptar devices in their study and weighed the devices before and after filling with the IN formulation as well as before and after actuation. Surprisingly, Tylleskar et al. (2017) found that the actual filling volume was 6% less than advertised by Aptar and the spray volume reduced by about 7%. If we assume that these Aptar device inaccuracies occur across studies, then we need to consider that IN bioavailability may be slightly underestimated across studies, given that AUC comparisons were possibly conducted for only 93% (i.e. 100% minus 7%) of the IN dose versus 100% of the parenteral dose. This potential issue needs to be quantified and taken into account.

Moreover, while the findings in the chapter support good early absorption and overall bioavailability in healthy subjects, concentrated naloxone nasal spray has yet to be formally tested in the target population of opioid users (see also Chapter 10).

8.4.3 Possible mechanisms and implications for clinicians

In recent years, international clinical practice has seen a shift from IV to IM naloxone for greater ease of administration, given that venous access can be difficult to establish in long-term injecting drug users (EMCDDA, 2016a). IV administration leads to an immediate increase of plasma naloxone levels with early Tax, high Cmax, and rapid decline in plasma concentrations thereafter. By comparison, IM administration produces slower absorption (i.e. later Tmax) and lower Cmax. However, the plasma profile following IM administration is now increasingly considered therapeutically beneficial: it avoids the extreme spike of IV naloxone but still attains efficacious plasma levels within the first minutes post-dosing; I have additionally studied the T50% parameter for this very reason. Furthermore, the longer duration of effect of IM naloxone is may protect against re-narcotization (Vilke, Sloane, Smith, & Chan, 2003).

Overall, the results of this chapter point to the worth of concentrated IN spray for opioid overdose reversal. The 2mg IN dose matched the early exposure (AUCp) from the 0.4mg IM reference, but maintained plasma levels at the approximate level of two 0.4mg IM doses for over two hours post-dosing. Plasma concentrations from the 2mg IN dose exceeded those from 0.4mg IM injection within 6 minutes post-dosing on average (see Figure 30).

The repeat dose simulations in this chapter highlight the potential for dose-titration using the 2mg IN dose. The focus on this 2mg IN dose may be particularly applicable to emergency administration using a dose-escalation schedule such as recommended with IM doses (EMCDDA, 2016a; UKMi, 2016; WHO, 2011b), starting at 0.4mg and increased at intervals (e.g. 3-minute intervals) to a total of 2mg. A comparable IN dose-escalation schedule would involve an initial 2mg dose to achieve onset comparable to IM 0.4mg, followed by a second 2mg IN dose three minutes later; this is the hypothetical schedule examined in the repeat-dosing simulation. Since the second IN dose is given to the unused nostril, absorption from both administrations should be equal, and the similarity between the simulation and the 4mg tested dose supports this assumption. Furthermore, the sustained plasma concentrations for the 2mg IN dose compared with the IM reference may benefit post-resuscitation care. Given that the half-life of some opioids substantially exceeds that of naloxone (1-1.5h) (WHO, 2014) (see also Chapter 1), sustained plasma naloxone concentrations from IN administration would likely reduce the risk of rebound toxicity when naloxone concentrations drop following IV or IM administration. The longer duration of action of IN naloxone and its potential for dose titration may therefore be of clinical value especially for the reversal of overdoses from synthetic opioids with long half-life duration (e.g. methadone).

The possibility of dose titration also presents distinct advantages in the community setting. Incremental dose titration could significantly reduce the risk of adverse reactions. High initial naloxone doses may trigger severe sudden-onset opioid withdrawal (Buajordet et al., 2004; WHO, 2014). A recent qualitative analysis of cases of heroin/opioid overdose reversals identified apparent excessive naloxone dosing ('over-antagonism'), sometimes triggering patient self-discharge and active further drug-seeking (Neale & Strang, 2015). In addition to pharmacological toxicity, such 'behavioral toxicity' needs to be considered. Withdrawal symptoms can be particularly challenging for overdose witnesses to manage in the community setting. Simulation of repeat administration of the 2mg IN dose produced roughly equivalent plasma naloxone levels as a single 4mg IN dose. Giving a single 2mg IN dose at first and following up with a second 2mg IN dose only if needed could lower the risk of naloxone 'over-antagonism' and improve the safety of the overdose victim and those attending the overdose scene. In addition, if naloxone doses trigger frequent severe withdrawal symptoms, then there is a real danger that, despite its life-saving value, naloxone may be viewed as a punitive medication that is to be avoided, as was the perspective of many overdose patients interviewed (Neale & Strang, 2015). This might be regarded as 'reputational toxicity'.

8.4.4 Possible mechanisms and implications for policymakers

In terms of policy implications, a naloxone nasal spray licensed by the European Medicines Agency may in future have potential for classification as over-the-counter medication, as it would not be subject to Article 71 of the EU Medicinal Products Directive (2001/83), according to which injectable medicinal products are by definition prescription-only medications (EMCDDA, 2016a).

8.4.5 Questions for future research

Regulatory authorities – when deciding about the potential approval of novel formulations of already licensed drugs – require evidence of overall drug exposure (AUC), bioavailability, the maximum dose achieved (Cmax) and time between dosing and Cmax (tmax). While the above PK data for the Mundipharma nasal spray formulations, particularly the 2mg/0.1mL dose, look promising, at least four unanswered questions remain that will likely be relevant to regulatory review and future research.

The first two address naloxone use in clinical practice in general, whereas the final two questions relate to the need for naloxone research in special patient groups.

Impact of Cmax

In relation to the 0.4mg IM reference, the Cmax of the 2mg IN dose was substantially higher and roughly equivalent to a 1mg IM dose. Even though the early partial AUC values were similar for 0.4mg IM and 2mg IN, the elevated IN Cmax may pose a potential reason for concern, as dose-related adverse effects often occur around the Cmax (Rang et al., 2012). As described in Chapter 1, the British National Formulary (BNF) recommends repeat administration (if necessary) of 0.4mg IM doses at 2-3 minute intervals for non-medical settings (BNF, 2017). In the exploratory repeat dosing simulations, administration of two 2mg IN doses was scheduled at a 3-minute interval, displaying similar peak plasma concentration (approximately 5.5 ng/mL) as five 0.4mg IM doses also administered at 3-minute intervals. It is unclear if these simulated peak plasma concentrations would induce adverse effects in opioid overdose victims.

In an Australian ambulance-based randomized trial (Kelly et al., 2005), which assigned 155 opioid overdose victims to receive either 2mg IM or 2mg/5mL IN naloxone, minor adverse reactions (agitation/irritation, nausea/vomiting, headache, tremor, sweating) were more common in the IM group (21%) than the IN group (12%), but this difference may have been due to the dilute nasal formulation used. For concentrated naloxone nasal spray, the pharmacodynamic effects of the Cmax and the optimal timing for repeat dosing have yet to be empirically tested.

Time-to-naloxone administration

My exploratory analysis of early naloxone absorption showed that the 2mg IN dose took, on average, two minutes longer than the IM reference (6 versus 4 minutes) to reach 50% Cmax of the IM reference ($T50_{REF}$%). It is unclear what implications this 2-minute delay may have in out-of-hospital settings.

The administration of injectable naloxone presents multiple logistical challenges, such as the fear of needle/syringe preparation and injecting procedures, the potential absence of a sterile syringe, or insufficient training in needle-and-syringe assembly, which can all delay the time to drug administration for the intramuscular naloxone injection (Beletsky et al., 2012; EMCDDA, 2016a). In their review of naloxone products licensed in the UK, the UKMi (2016) noted that for layperson use of pre-filled syringes for IM administration "some manipulation will be required to attach the needle to the product".

Consideration needs to be given to how quickly the nasal spray versus injectable naloxone can be administered, which then needs to be considered alongside

pharmacokinetics-derived speed of onset. It is possible that the speed of administration of the nasal spray may be quicker than administration of an IM injection, so that the 2-minute delay may be partially or fully offset. Measurement of the time involved in preparing and administering the device is largely absent from current considerations of different naloxone formulations. An early exception is Wanger and colleagues' ambulance study (1998) of subcutaneous naloxone: the time from arrival at the patient's side to dose administration was 4 minutes (subcutaneous) versus 6 minutes (IV). Inclusion of these time intervals is essential for consideration of the merits of different routes of administration, especially in case of layperson administration. Future studies should examine the time to naloxone administration for different devices when used by laypersons without medical training. Such studies could assess whether the slightly earlier onset of IM administration seen in the results of this chapter may be offset by potentially better usability of the nasal spray device.

Impact of nasal damage

In the study reported in this chapter, healthy volunteers underwent nasal passage examination at screening, pre- and immediately post-dose, and any nasal irregularity was considered a reason for exclusion. The pharmacokinetics of the naloxone nasal spray formulations were thus tested under optimal conditions. However, nasal naloxone might be absorbed differently by opioid users in whom the nasal mucosa may be compromised (e.g. due to chronic ulceration from drug snorting (Peyrière et al., 2013)) or obstructed from mucus or from vomit during overdose (Strang, McDonald, et al., 2016). At a practical level, it is challenging to quantify the impact of nasal congestion or mucosa damage, both in terms of possible reduction in, or alternatively enhancement, of absorption (Arora, Sharma, & Garg, 2002).

Only one study has been conducted which investigated the pharmacokinetics of nasal naloxone in a special patient group. Using a randomized crossover design, Edwards et al. (2016) compared an IM injection (2mg/2mL) to two nasal spray conditions in patients with chronic rhinitis (n=36): one nasal treatment involved dilute IN naloxone on its own (2mg/2mL, with 1mg/mL per nostril), whereas the other treatment comprised the same IN naloxone dose but preceded (30 minutes prior) by pretreatment with a nasal decongestant spray (oxymetazoline, dose not reported). Pretreatment with oxymetazoline led to a delayed IN tmax (20 minutes versus 15 minutes) and reduced relative bioavailability of IN naloxone from 15% to 12% (based on AUCt). While these findings tentatively suggest that nasal congestion might be associated with slightly

enhanced IN naloxone absorption, they need to be interpreted with great caution. The study did not include a healthy control group, and it is thus impossible to draw causal conclusions on the effect of rhinitis on naloxone absorption.

Regarding compromised mucosa from drug snorting, it is unclear how prevalent nasal mucosa damage from heroin snorting may be, as only limited data are available. A single case series of 24 chronic intranasal heroin users has been published, whose complications comprised nasal perforation (11 cases), nasal ulceration or erythema (5 cases), nasal septum necrosis (5 cases), pharyngeal ulceration (3 cases), and palate damages (5 cases) (Peyrière et al., 2013). It should be noted that heroin snorting is relatively uncommon (EMCDDA, 2016), with injecting and smoking constituting the most prevalent routes of heroin use (Barrio et al., 2001; Novak & Kral, 2011). There is thus greater likelihood of nasal damage in opioid overdose victims resulting from the snorting of other drugs, such as cocaine. The link between cocaine snorting and nasal damage is well documented. For instance, in an Italian sample of more-than-weekly cocaine users, about 10% had nasal septal perforation (Businco et al., 2008).

Clinical evidence suggests that the risk of modified absorption of IN naloxone may be small: In an Australian ambulance-based randomized trial (Kelly et al., 2005) which assigned patients with suspected opioid overdose (n=155) to naloxone treatment of either dilute nasal spray (2mg/5mL) or 2mg/2mL IM injection, there was no significant group difference regarding the need for a rescue injection of naloxone. Nonetheless, future research should systematically study the impact of temporary or chronic nasal abnormalities on the absorption of concentrated nasal naloxone.

Impact of liver damage

In the UK, injecting drug use constitutes the main risk factor for hepatitis C virus (HCV) transmission, as approximately half of current or recent injecting drug users are infected with HCV (Budd & Robertson, 2005; Martin et al., 2012; Nelson et al., 2011). Hepatitis and other forms of liver disease affect the pharmacokinetic behavior of many drugs, with the largest impact seen for drugs that are normally characterized by high first-pass metabolism, such as naloxone (Weeks & Tomlin, 2006). In patients with liver disease and hepatic impairment, first-pass metabolism is reduced, which leads to increased drug bioavailability.

In healthy individuals, naloxone is rapidly metabolized when it reaches the liver. As discussed in Chapter 1, orally administered naloxone has a very low bioavailability of <2% (Smith et al., 2012). Similarly, in Chapters 6 and 7, sublingual naloxone only had

2% bioavailability, presumably because the naloxone solution was swallowed (Mundin, McDonald, et al., 2017).

In patients with moderate and severe hepatic impairment, significantly elevated plasma naloxone levels have been observed following sublingual naloxone administration (Nasser et al., 2015). Nasally administered naloxone largely avoids the first-pass metabolism. However, once nasally administered naloxone is available systemically, it is possible that hepatic impairment may influence its metabolic clearance. It is unclear to what extent naloxone bioavailability from nasal administration may be increased in patients with hepatic impairment and whether this may be associated with an elevated risk of adverse events.

In the US, where about three quarters of injecting drug users are infected with HCV (Nelson et al., 2011), 245 cases of administration of the FDA-approved 4mg nasal spray (NARCAN® by Adapt; see Chapter 4) reportedly led to withdrawal syndrome in 14% of overdose victims (Fiore, 2017). It is reasonable to assume that the incidence rate of withdrawal associated with a 2mg IN dose would be lower. However, it is unknown how many (if any) of these 245 cases of suspected opioid overdose suffered from hepatic impairment.

In future, a pharmacokinetic study of nasal naloxone administration in (non-opioid using) patients with degrees of hepatic impairment could provide more accurate data.

8.5 Conclusions

Taken together with other recently published data (Krieter et al., 2016; Mundin, McDonald, et al., 2017; Tylleskar et al., 2017), the results of this chapter lend strong support to the potential value of concentrated IN naloxone spray for opioid overdose reversal. Across all three IN doses, naloxone exposure was dose-proportional, with approximately 50% absolute bioavailability. The 2mg/0.1mL IN dose was most similar to the 0.4mg IM reference, producing comparable early partial naloxone exposure, indicating they would also deliver comparable therapeutic concentrations in the event of an opioid overdose. The 2mg IN dose had the added feature of potential benefit of stronger maintenance of plasma levels for the next two hours. During my industry placement at Mundipharma, the company submitted a product portfolio for the 2mg IN dose to the European Medicines Agency for regulatory approval, framing the spray as a product “developed to combine the advantages of an effective dose of naloxone with user-friendly IN administration, in a form that can be given by anyone (medically-trained

or otherwise) needing to help [an opioid overdose victim] […] before emergency healthcare can be provided" (Mundipharma, 2016).

At the time of writing, it is anticipated that the European Medicines Agency may approve a first nasal naloxone spray by late 2017 or early 2018. If a naloxone nasal spray (i.e. the Mundipharma 2mg/0.1mL formulation or a similar product by other manufacturers) receives regulatory approval in Europe, clinicians and policymakers will need to consider the potentially different merits of the various time-course profiles (including speed of onset and duration of effect) of IN versus injectable naloxone and may also see implementation advantages with IN naloxone for broad-based take-home naloxone provision.

Following the pharmacokinetic analysis of intranasal naloxone formulations in this chapter and in preceding Chapters 6 and 7, the next chapter will describe the development and preliminary testing of a novel buccal naloxone tablet.

Chapter 9 Beyond Nasal: The Exploration of Buccal Naloxone

Preface

In Chapter 5, I explored the buccal, sublingual, and nasal routes of administration as candidates for non-injectable naloxone delivery for opioid overdose reversal. While Chapters 6 to 8 focused primarily on concentrated nasal formulations, this chapter explores the potential of buccal naloxone delivery.

As part of my PhD project, my supervisors and I were involved in the development of a novel buccal naloxone tablet, in collaboration with Professor Ben Forbes, Dr. Paul Royall, and Dr. Abdulmalik Alqurshi from the Institute of Pharmaceutical Science at King's. In 2015, the university applied to register intellectual property on the buccal naloxone tablet formulation. A copy of the international patent application (WO2016/146981 A1) is included in Appendix C and lists me as co-inventor.

This chapter comprises content from my November 2015 presentation ("Buccal naloxone for opioid overdose reversal: rationale for and development of a novel instant-dissolving tablet formulation") at the Neuroimaging and Experimental Medicine conference at IoPPN, for which I received a poster award, as well as from my co-authored paper ("Amorphous formulation and in vitro performance testing of instantly disintegrating buccal tablets for the emergency delivery of naloxone") that was published in Molecular Pharmaceutics (Alqurshi et al., 2016).

I have divided the chapter into five sections. The first part describes the rationale behind the design of a buccal naloxone tablet. The development and composition of the buccal tablet are summarized in the second part of the chapter, and the third part reviews its in vitro properties. The fourth part of the chapter addresses plans for in vivo testing. Two clinical trials of the pharmacokinetics of buccal naloxone administration were originally planned as empirical basis of my PhD project. Unfortunately, these clinical trials faced several internal regulatory obstacles and never reached the data collection stage. The reasons for the failure to complete the trials are provided in the fifth and final section of this chapter which discusses the challenges of conducting this work.

9.1 Rationale

Oral tablets can constitute low-cost and highly portable medical technologies. However, orally ingested naloxone dosage forms are unsuitable as they are not easily administered to an unconscious patient. Moreover, orally ingested naloxone has low bioavailability (< 1%) as a result of high first-pass metabolism (Fishman et al., 1973; Hussain et al., 1987) (see Chapters 1 & 5).

By contrast, with its lack of hepatic and gastrointestinal first-pass effect, buccal delivery provides an attractive alternative route of administration for the emergency delivery of drugs (Lam et al., 2014; Sankar et al., 2011; Sudhakar et al., 2006). The buccal route is particularly useful for drug delivery in unconscious patients. Even in the case of jaw lock in the patient, the buccal cavity is easy for bystanders to access, and application of a dosage form (e.g. tablet) to the inner cheeks of the oral cavity is simple and can be precisely located (Sudhakar et al., 2006). In case of drug toxicity or adverse reactions, buccal dosage forms can also easily be removed. Dosage forms for buccal delivery include (i) tablets and lozenges, (ii) films, wafers and patches, (iii) liquids, creams, gels, ointments, (iv) sprays, lozenges, chewing gum and mucoadhesive film (Patel et al., 2011).

Buccal delivery has been proven effective in other pharmacotherapies, e.g., buccal midazolam (“Buccolam”) for the treatment of epileptic seizures and agitation (McIntyre et al., 2005; Schwagmeier et al., 1998; Taylor et al., 2008). Buccolam produces rapid onset of action and has a mean bioavailability of 75% (Schwagmeier et al., 1998). It is now a licensed treatment that bystanders can administer while awaiting professional medical care (MHRA, 2011).

In rats, naloxone bioavailability from buccal administration has been reported to be 70%, compared to 0.3% via the oral route, with maximum plasma levels obtained within 15 min (Hussain et al., 1987). However, the absorption of naloxone from the human buccal cavity is unknown.

For buccal naloxone administration in humans, tablets may provide a suitable dosage form. Among the above described options for buccal dosage forms, tablets provide the simplest, most portable and easily applied formulation as an emergency medicine. However, immediate dissolution of the tablet upon application will be crucial for clinical efficacy in the opioid overdose emergency. Speed of onset is critical to reverse the life-threatening respiratory depression which characterizes the opioid overdose (see Chapter 1).

The aims of this chapter are threefold:

- Aim 1: To develop a buccal tablet that contains a clinically relevant naloxone dose and dissolves instantly (e.g. ≤ 30 s);
- Aim 2: To test the stability and dissolution of the tablet in vitro;
- Aim 3: To prepare for PK study of buccal naloxone administration in humans.

9.2 Tablet specifications and development

At the start of my PhD, I was involved in discussions with my supervisors and project partners Professor Ben Forbes, Dr. Paul Royall, and Dr. Abdulmalik Alqurshi (himself a PhD student at the time) around the desired properties of a buccal naloxone tablet. We had agreed on the aim to develop a safe, easily administered, buccal tablet which would be suitable for the rapid delivery of naloxone in opioid overdose. The following product design specifications were drawn up:

The size and shape of the buccal tablet would need to ensure a high surface area contact with the buccal epithelium to maximize naloxone absorption, and the physical structure of the tablet would need to allow for 'instant' naloxone liberation and dissolution rates (e.g. ≤ 30 s) to be suitable as emergency medicine. Determination of the target dose was challenging. There was no data on buccal naloxone administration in humans, and existing published pharmacokinetic or pharmacodynamic studies of parenteral or intranasal naloxone did not enable simple determination of the appropriate dose required to achieve a target concentration or concentration–time profile to maximize its antidote efficacy (Dowling et al., 2008; Preston et al., Loimer et al., 1994). The naloxone dosing algorithm by Clarke et al. (2005) recommended an initial intramuscular or subcutaneous dose of 0.4-0.8mg. Similarly, the WHO guidelines (2014) noted that [parenteral administration] of 0.4-0.8mg naloxone was an effective dose in most cases (see also Chapter 1). Similarly,

Preclinical research had found buccal naloxone bioavailability of up to 71% in non-human animals (Hussain et al., 1987; Hussain et al., 1988) (see also Chapter 5). Therefore, 0.8mg, i.e. the upper limit of the dose range recommended by WHO (2014), was chosen as target dose for the buccal naloxone tablet: if buccal naloxone bioavailability in humans was anywhere between 50-100%, then naloxone exposure from a 0.8mg buccal tablet should equate to naloxone exposure from a 0.4-0.8mg parenteral dose range.

9.2.1 Tablet manufacture

Instant-dissolving tablets buccal naloxone tablets were successfully developed using freeze-drying technology (lyophilization). The tablets were produced at the Institute of Pharmaceutical Science and later also, in accordance with ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) guidelines, in the Pharmacy Manufacturing Unit of Guy's Hospital of the Guy's and St Thomas' NHS Foundation Trust. The development and optimization of the tablets has been described in depth by Alqurshi et al. (2016). To review briefly, the manufacture of the tablets (with a yield of 20 tablets per batch) involved five key steps:

1. Feed solution for tablet preparation was prepared by dissolving gelatin powder (Fagron Ltd), sodium bicarbonate powder (Fagron Ltd; Newcastle upon Tyne, UK) and mannitol (Fresenius Kabi; Runcorn, UK) in water for injection (WFI) held at 70^{o}C.
2. Once the feed solution had cooled down to room temperature, naloxone hydrochloride dihydrate (Fagron Ltd) was dissolved in it.
3. The naloxone hydrochloride feed solution (1.500 g each) was filled into empty aluminium blister wells (Zhejang Xinfei Machinery Ltd; Zhejiang,China) and cooled down to -80^{o}C.
4. Frozen tablets where transferred from the blister wells into pre-cooled freeze-drying vials (1 oz. Clear Glass Universal Type 1), and a 5-day freeze drying cycle inside a temperature controlled freeze-drying chamber (Lyotrap freeze dryer; LTE Scientific Ltd; Oldham, UK) at -40^{o}C was initiated.
5. At the end of the freeze-drying cycle, the freeze-drying vials containing the tablets were sealed under nitrogen for protection.

9.2.2 Tablet composition and dimensions

Tablet composition was optimized as follows: Ratios of mannitol, gelatin and sodium bicarbonate were varied with the aim of identifying a tablet composition that would form a non-crystalline solid freeze-dried product. Mannitol was utilized because of its hydrophilic nature, bulking properties, and protective function for freeze-dried material (Jawad et al., 2012). Gelatin was selected to provide structural strength, and it has mucoadhesive properties. Sodium bicarbonate was added to reduce crystallization within the tablets. Thus, an optimized formulation with a composition of 24% w/w mannitol, 65% w/w gelatin and 11% w/w sodium bicarbonate and target drug content of 0.8mg of Naloxone HCl per tablet was defined. The tablets were white in color, 29.4 ± 0.2mm in

length, 16.1 ± 0.5mm in width with a depth of 3.0 ± 0.2mm and weighed 17.7 ± 0.4mg (see Figure 33).

Figure 33 The instant dissolving tablet with display of its length in mm (left) and intended application method (right)

Table 30 Instant dissolving tablet specification and stability data (mean, SD)

		Stability		
		0 months	9 months	9 months
Parameter	Specification		4°C	25°C
Tablet weight (mg)	16.9 - 20.7	17.8 ± 0.5	17.8 ± 0.5	17.6 ± 0.5
Dimension - length (mm)	20.0 - 30.0	29.4 ± 0.2	29.1 ± 0.3	29.1 ± 0.7
Dimension - width (mm)	14.0 - 18.0	16.1 ± 0.5	16.1 ± 0.3	16.0 ± 0.3
Disintegration test (s)	≤180	14.0 ± 5.9	9.0 ± 5.0	10.0 ± 5.0
Naloxone HCL assay (mg)	0.76 - 0.84	0.80 ± 0.01	0.81 ± 0.02	0.80 ± 0.03

Annotation: 3 batches of n=2 each, i.e. 6 data points in total were used for stability testing.

9.3 In vitro testing

The following in vitro tests were performed by Dr. Abdulmalik Alqurshi as part of his PhD project at the Institute of Pharmaceutical Science, and the methodology is described in detail in our joint publication (Alqurshi et al., 2016).

9.3.1 Stability

To ensure standard delivery of a dose of 0.8mg ±5% of naloxone, the buccal tablet was tested for chemical and physical stability.

As part of quality control, a tablet specification was developed for weight, dimensions, rate of disintegration and drug content and used to verify batch-to batch reproducibility and stability (see Table 30). The instant dissolving buccal tablets matched the quality specifications for weight, size, speed of dissolution and drug content at baseline and were physically stable over 9 months when stored under nitrogen at 4^{o}C or 25^{o}C.

A validated reverse phase HPLC assay for naloxone hydrochloride was used to assess chemical stability at 9 months, and the target drug content, 0.8mg of naloxone hydrochloride per tablet was confirmed (range: 0.80 ± 0.03mg; see Table 30).[30]

9.3.2 Dissolution

Tablet dissolution testing was conducted to provide information on drug release for quality control purposes and to potentially predict in vivo performance. Since speed of naloxone liberation is critical for a buccal tablet designed for emergency use in opioid overdose, a novel digital imaging-based dissolution assay (see Figure 34) was developed to represent the temperature and saliva volume conditions in the buccal cavity: i.e. a temperature range of 33-37^{o}C was tested in combination with dissolution volumes in the range of 0.1-0.7mL (see Figure 35) (DiSabato et al., 1996; Moore, 1999). This volume range was chosen because a volume of 0.7mL of oral fluid is typically available in the buccal cavity of adults, but the volume may be reduced in opioid users and in opioid overdose (Patel, Liu, & Brown, 2012). Two types of dissolution medium were tested: phosphate buffer and a synthetic saliva (consisting of mucin 2.16 g/L from porcine stomach, distilled water, and salts) (Quilaqueo et al., 2015). Dissolution was measured using a camera located above a test blister well (with its background painted black to provide contrast for the white tablet) which would take a reference image (blister filled with dissolution medium) before testing and then, a baseline image (t = 0 seconds) once the table was placed in the dry blister, and a series of 100 test images at 0.4 second intervals once the dissolution medium was added (e.g., 0.7mL distilled water at 35^{o}C). Assay temperature was adjusted by use of a temperature-controlled water bath. The effects of temperature, solvent volume and composition on the dissolution of the tablets were as follows: The tablets dissolved fully (>90%) within 30 seconds under all conditions. Tablets dissolved in <10 seconds in 0.7mL of phosphate buffer at 35^{o}C (see Figure 35, A). Temperature variation over 33-37^{o}C (i.e. the range reported to exist in the

buccal cavity) did not alter the dissolution rate, but the rate was 4-5 times slower at 25^{o}C. Reducing the dissolution volume progressively reduced the rate at which the tablet dissolved, with dissolution in 0.1mL being 4.5 times slower than in 0.7mL (see Figure 35, B). Interestingly, when phosphate buffer was replaced with synthetic saliva, a slightly quicker dissolution rate was observed (see Figure 35, C), suggesting that human in vivo performance would likely be quicker than the phosphate buffer curves.

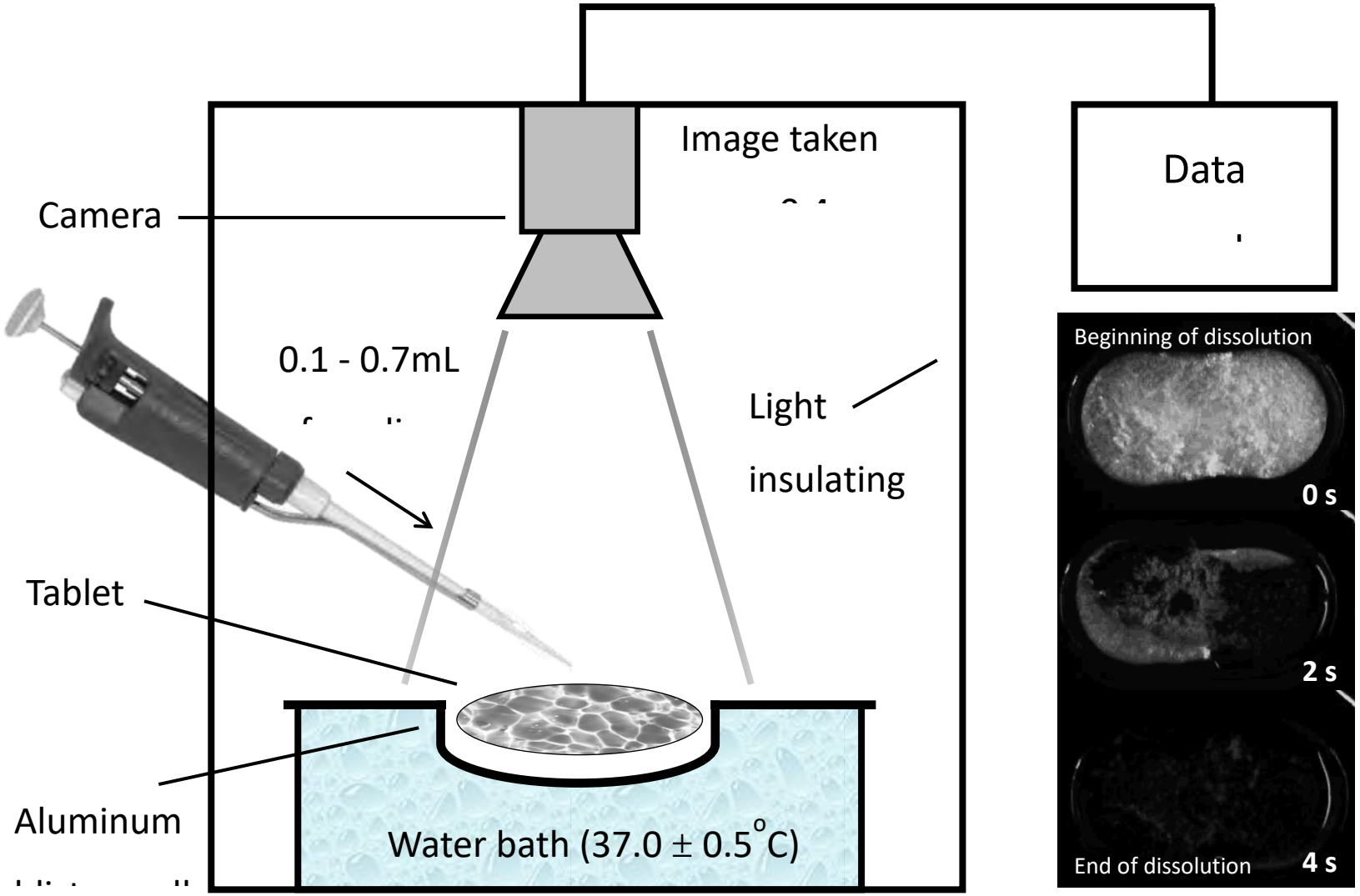

Figure 34 Digital imaging dissolution assay

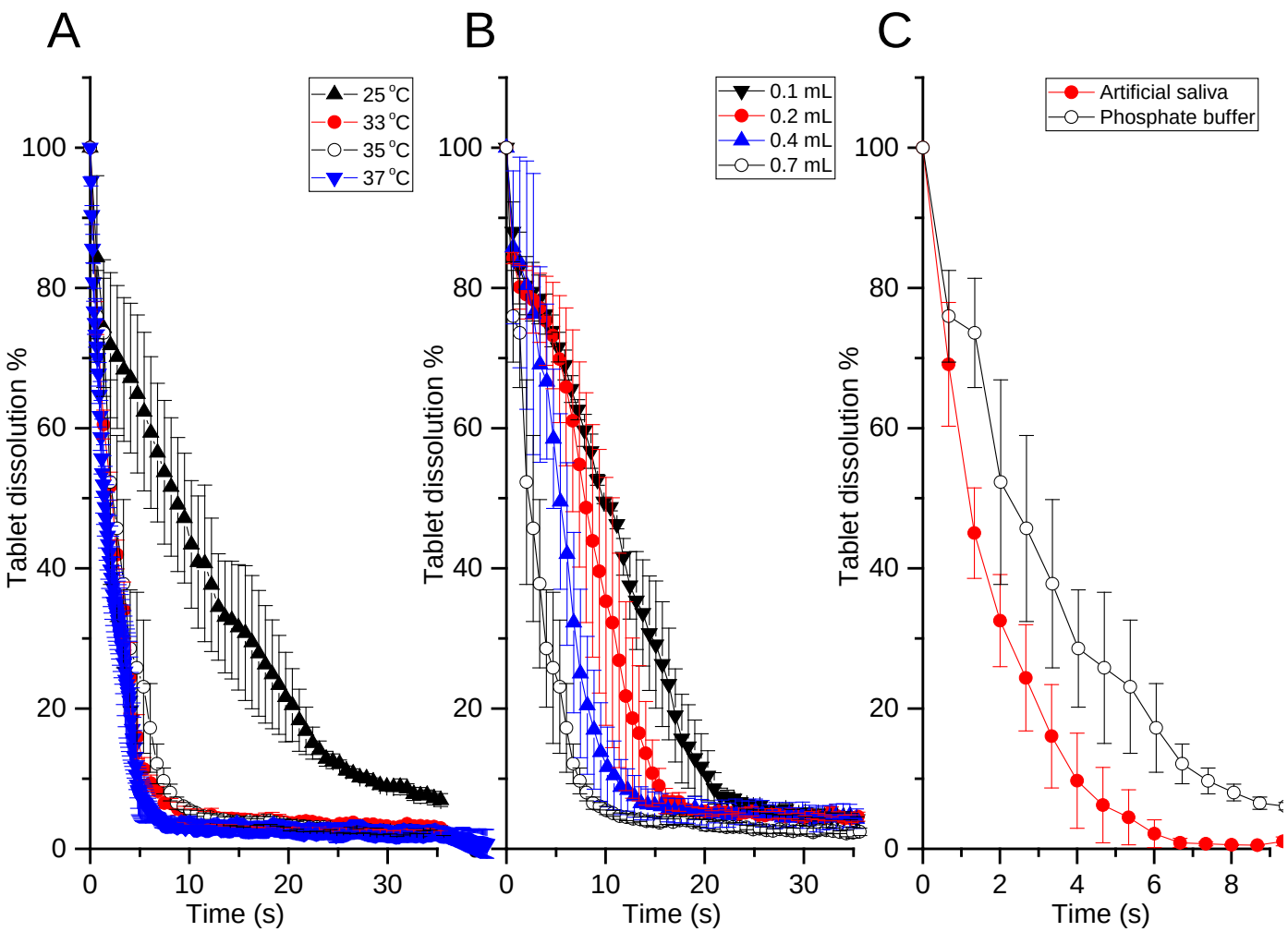

Figure 35 Effect of temperature, fluid volume, and dissolution medium on tablet dissolution

9.4 Plans for in vivo testing

As part of my PhD project, I planned two first-in-human clinical trials of buccal naloxone administration. Both trials were devised as Phase-I healthy volunteer studies that would generate buccal naloxone pharmacokinetics data. Since buccal administration of neither licensed naloxone-hydrochloride solution nor the novel naloxone tablet had been tested in humans before, both studies were classified as CTIMP (Clinical Trial of an Investigational Medicinal Product). My role involved the following responsibilities: overall study coordination; application for risk assessment and EudraCT registration; application for ethical, MHRA, and R&D approvals; (participant recruitment; data collection; data management and analysis). Due to regulatory obstacles, the trials did not reach the recruitment stage (see Table 31).

9.4.1 Rationale

The first clinical trial (EudraCT number 2014-001802-16) was designed to provide proof-of-concept for buccal administration by examining absorption of licensed naloxone hydrochloride solution from the buccal cavity. The second clinical trial (EudraCT number 2016-000582-23) would assess naloxone exposure from the buccal tablet (see above). Both trials would compare the pharmacokinetics of a single and multiple 0.8mg doses of buccal naloxone relative to a 0.8mg dose of licensed naloxone-hydrochloride solution by intravenous and intramuscular injection. As such, the trials would assess whether naloxone absorption from the buccal naloxone tablet is sufficiently rapid and dose-related and would contrast naloxone exposure from the buccal solution versus tablet formulation.

9.4.2 Aims

The aims of the two clinical trials were as follows:

- Aim 1: To determine and compare overall naloxone exposure and bioavailability from buccal administration compared to the licensed IM and IV routes of administration.
- Aim 2: To identify an optimal dosage range (based on onset of action and maximum concentration) for the buccal naloxone administration.
- Aim 3: To assess whether naloxone absorption from the buccal tablet is sufficiently rapid and dose-related to be relevant to emergency treatment of heroin/opioid overdose.

9.4.3 Study design

Both trials were devised an open-labelled, 4-period, randomized crossover design in healthy volunteers. The distribution of the 4 treatments would follow a Latin square design, where each treatment occurs only once at each position of the treatment sequence and only once for each subject (see also Chapter 7). The crossover design was considered appropriate as the half-life of naloxone is known (1±0.5 hours, see Chapter 1) and the washout period of at least 3 days was deemed sufficient to mitigate against any carryover effects. The similarities and differences in the study design of the two trials are outlined in Table 31.

9.4.4 Dose justification

The proposed buccal naloxone doses (0.8-3.2mg) were below the dose approved by the FDA for Adapt naloxone nasal spray (4mg) (FDA, 2015). Buccal naloxone availability was estimated to fall into the range of 16-75% based on prior research which had found 16-71% buccal bioavailability of naloxone in non-human animals (Hussain et al., 1987; Hussain et al., 1988) and 65-75% buccal availability of other active ingredients (fentanyl, midazolam) in humans (Loetsch et al., 2013; Schwagmeier et al., 1998). The referenced studies had found buccal availability to be lower than nasal bioavailability (i.e. for naloxone, fentanyl, midazolam) across species. The upper buccal naloxone dose of 3.2mg in Trial 2 (administered bilaterally as four 0.8mg tablets) was also chosen for tablet development reasons: if the trial were to indicate that buccal naloxone availability was low, then the naloxone content of the buccal tablet would in future likely need to be increased to a dose higher than 0.8mg. In terms of tablet formulation, it was expected that the lyophilized tablet could potentially be loaded with a naloxone content of up to 3.2mg, and it was therefore considered useful to study the pharmacokinetics of this upper dose. Naloxone-related adverse events were not expected at the proposed doses (0.8-3.2mg), as naloxone does not have any pharmacological effects in non-opioid using healthy volunteers (see Chapter 1). There is limited clinical experience with naloxone overdose in humans, and adverse events in non-opioid users have only been reported for doses ≥2mg/kg of bodyweight. The buccal doses for administration in the two trials were therefore considered safe and reasonable to meet the study objectives.

Table 31 Comparison of the buccal naloxone clinical trials

	TRIAL 1: **Buccal solution (pilot)**	**TRIAL 2:** **Buccal naloxone tablet**
Title	A Pilot, Phase 1, Open-Labelled, 4 Period, Randomised, Crossover Study to Evaluate the Pharmacokinetics of Naloxone when Given by the IV, IM and Buccal Routes of Administration in Healthy Male Subjects	A Pilot, Phase 1, Open-Labelled, Randomised, Crossover Study to Evaluate the Pharmacokinetics of Naloxone in Healthy Male Subjects when Given by a Novel Buccal Tablet Compared to IV and IM Administration
EudraCT	2014-0001802-16	2016-000582-23
Clinical phase	Phase I	idem
Investigational site	Clinical Research Facility King's College Hospital London SE5 9RS	idem
Study design	open-labelled, 4-session, randomized crossover (Latin square)	*idem*
Duration of treatment	4 doses over a maximum of 4 weeks	*idem*
Treatments	• 0.8mg buccal solution[1] • 1.6mg buccal solution[1] • 0.8mg IM injection[2] • 0.8mg IV injection[2]	• 0.8mg buccal tablet[1] • 3.2mg buccal tablet[1] • 0.8mg IM injection[2] • 0.8mg IV injection[2]
[1]Test product	Prenoxad® 1mg/ml naloxone hydrochloride injection (manufactured by Martindale Pharmaceuticals Ltd.), squirted into the buccal pouch	0.8mg buccal naloxone tablet (manufactured by the Pharmacy Manufacturing Unit, Guy's Hospital); 3.2mg dose = 4 x 0.8mg tablets
[2]Reference product	Prenoxad® 1mg/ml naloxone hydrochloride injection (manufactured by Martindale Pharmaceuticals Ltd.)	idem
Number of subjects	n = 4	n = 8
Eligibility	Healthy male volunteers: - Age 18–64 years - BMI of 19–29.9 kg/m^2. Without previous or current opioid dependence or abuse, current use of opioid analgesics for pain relief, or any current or recent oral tract infection or lesion.	*idem*
Blood collection schedule	-5, +1, 2, 3, 4, 6, 8, 10, 12.5, 15, 30, 45, 60, 75, 90, 120, 150, 180, 240, 300, 360, 420, 480 minutes	i*dem*
Outcomes	Pharmacokinetics: F%, AUC, T_{max}, C_{max}, $T_{1/2}$ Safety: Adverse events, vital signs	*idem*
Regulatory approvals		
IoPPN risk assessment	Yes (July 2014)	Yes (April 2015)
MHRA	Yes (November 2014)	X
Ethical approval	Yes (March 2015)	X
KCH R&D	X	X

9.4.5 Study population

Target enrollment involved healthy male subjects aged 18 to 64 years, with n=4 (maximum enrollment of 6 subjects, in case of withdrawals from the study) for the pilot and n=8 (maximum 12 subjects) for the tablet study. Females were excluded, as the safety of buccal naloxone during pregnancy has not been established.

9.4.6 Study procedures

Since both trials were considered first-in-human studies, the NIHR and Wellcome Trust King's Clinical Research Facility, which provides direct access to King's College Hospital, was proposed as investigational site. Subjects would be screened at least 14 days prior to the first treatment period. Subjects would be admitted to the Clinical Research Facility on the morning of each treatment Period and would remain under medical supervision until the 8-hour post dose assessment has been completed. Naloxone, in accordance with a pre-determined randomization sequence, would be administered on the morning of each treatment period. Serial blood samples for the assay of naloxone would be taken pre-dose and at specified time intervals up to 8 hours post-dosing (see Table 31). Subjects would be monitored for adverse events and remain under medical supervision at the Clinical Research Facility for a period of 8 hours post-dosing.

9.5 Challenges of conducting this work

The project faced many regulatory obstacles, which ultimately led to the early termination of the buccal naloxone pilot (EudraCT: 2014-001802-16) in July 2016. While the second trial which would assess the pharmacokinetics of the buccal tablet (EudraCT: 2016-000582-23) obtained clearance from the IoPPN risk assessment committee in April 2015, the study was never submitted for HRA or MHRA approval.

At the start my PhD in October 2013, the development of the buccal naloxone tablet was still ongoing, as the tablet composition was being optimized and tested in vitro (see above). To make use of the time needed for tablet development, I devised the protocol for a pilot study that would assess the pharmacokinetics of buccal administration of licensed naloxone-hydrochloride solution. The purpose of this pilot was to establish feasibility of naloxone delivery by the buccal route (see above), but also to serve as a dry run for the "main" trial involving the buccal naloxone tablet. The pilot would provide the opportunity to establish the high-frequency pharmacokinetic sampling method and validate the naloxone assay method

that was being developed by colleagues at the Toxicology Unit with the Department of Clinical Biochemistry at King's College Hospital.

Unfortunately, the delay associated with the regulatory obstacles of the buccal naloxone pilot developed a dynamic of its own, and neither of the two buccal naloxone studies managed to reach the data collection stage. The reasons for this failure are described in the following sections.

9.5.1 A clinical trial is a clinical trial is a clinical trial

The pilot study (buccal administration of licensed naloxone-hydrochloride solution vs. parenteral administration) required a full application to the Medicines and Healthcare Products Regulatory Agency (MHRA). Even though naloxone had been used in clinical practice for more than 40 years, and even though the pilot study was only going to recruit healthy volunteers in whom naloxone would not produce any pharmacodynamic effects (see Chapter 1), the MHRA classified the study as a Clinical Trial of an Investigational Medicinal Product (CTIMP), because naloxone was not licensed for use by the buccal route.

While I managed to secure MHRA approval in late November 2014, i.e. within just 14 months of the start of my PhD, the classification of the pilot trial as CTIMP triggered internal regulatory obstacles within King's Health Partners, i.e. the academic health science center comprising King's College London, Guy's and St Thomas', King's College Hospital, and South London and Maudsley (SLaM) NHS Foundation Trusts. As CTIMP, the pilot trial fell under the authority of the King's Health Partners Clinical Trials Office, which – unbeknownst to my supervisors and me – would have indirect and direct financial implications for the proposed buccal naloxone studies: The Clinical Trials Office uses performance targets for externally funded trials, which meant that externally funded trials were automatically prioritized over internally funded ones, and the processing times of internally funded studies (such as my pilot trial) were accordingly disadvantaged.

Moreover, the quality standards of the Clinical Trials Office apply to any CTIMP regardless its size. My planned naloxone studies with their sample sizes of only n=4-8 healthy volunteers had to meet the exact same criteria as a multi-site trial of a new active ingredient in hundreds of patients. While this principle may be logical and necessary from a research ethics perspective, it caused at least two specific practical issues.

Firstly, under King's Health Partners Clinical Trials Office guidelines, any clinical trial involving randomization is required to use the commercial randomization service of the

King's Clinical Trials Unit, which is part of the Department of Biostatistics. However, the randomization service of the Clinical Trials Unit charges a fee of £6.50 per subject, with a minimal charge of £650 (equivalent to 100 subjects) (CTU, 2017). For sample sizes of n=4-8 subjects, the charge for randomization would thus have equated to up to £162.50 per subject, for an open-label randomized crossover design in which each subject receives each treatment anyway.

Secondly, the King's Health Partners Clinical Trials Office requires any (de-identified) human subjects' data from a clinical trial to be stored on a validated eCRF (electronic Case Report Form) database. Data storage in Microsoft Access or Excel is not permitted since neither software produces an audit trail. Use of the King's Clinical Trials Unit's eCRF database service is recommended, but their minimum service charge for a UK-based single-site study is £7,340 (CTU, 2017). At 23 blood samples per participant and a sample size of n=4, this would have translated into a charge of £80 per data point in my buccal naloxone pilot trial.

At a combined minimum charge of £7,990 for data storage and participant randomization alone (in addition to the standard £3,400 MHRA application fee), these expenses would easily have exceeded the research funds of my PhD studentship. While my first supervisor and I eventually managed to negotiate exemptions from both regulations, nearly six months were lost in the process of these negotiations. Taken together, these issues raise the question whether CTIMPs are feasible as 3-year PhD projects.

9.5.2 Is a healthy volunteer a patient?

A separate issue – which ultimately caused the early termination of the pilot study – arose from the regulatory status of the proposed investigational site for both studies, i.e. the NIHR and Wellcome Trust King's Clinical Research Facility within King's Health Partners. The Clinical Research Facility is a shared facility of King's College London, Guy's and St Thomas', King's College Hospital, and SLaM NHS Foundation Trusts.

Geographically, the Clinical Research Facility is housed within King's College Hospital for a simple reason: in the event of adverse events, study participants can receive immediate medical care at the hospital. However, all study participants must pre-register as King's College Hospital patients so that, in case of an adverse event requiring treatment, participants can circumvent the waiting room of the emergency department and be directly transferred to the relevant clinical care unit within King's College Hospital.

The crucial question for the buccal naloxone pilot became: did healthy volunteers attending the Clinical Research Facility for data collection become NHS patients solely by pre-registering as King's College Hospital patients to allow for immediate treatment in the improbable event of an emergency? And if so, did healthy volunteer studies at the Clinical Research Facility require NHS co-sponsorship?

After submitting the protocol for the buccal naloxone pilot to the IoPPN Research & Development (R&D) office for initial risk assessment, the study was first assigned shared King's College London and SLaM NHS Foundation Trust co-sponsorship in August 2014, suggesting that healthy volunteers at the Clinical Research Facility were indeed considered NHS patients. However, just one month later, in September 2014, the IoPPN R&D office revoked its decision, stating that King's College London would be the sole sponsor as there was no NHS involvement. I subsequently submitted the protocol and related study documents to the MHRA and the National Research Ethics Service (NRES) for regulatory approval, with King's College London listed as sole sponsor of the proposed pilot study. Regulatory approvals from the MHRA and the National Research Ethics Service (REC 15/LO/0103, see Appendix A) were received in November 2014 and March 2015, respectively.

In May 2015, the King's Health Partners Clinical Trials Office convened a meeting with the King's College Hospital R&D office to clarify the regulatory status of studies using the Clinical Research Facility as investigational site. Following the meeting, I received notification from the King's Health Partners Clinical Trials Office that I would not need to apply to the King's College Hospital R&D office (as authority responsible for studies at the Clinical Research Facility) for full research governance approval; a confirmation letter from the Clinical Research Facility as investigational site and simple registration of the buccal naloxone pilot with the King's College Hospital R&D office would be sufficient. As advised, I applied to the King's College Hospital R&D for registration of the study, but my follow-up attempts over the course of the multiple months failed to elicit a response. My supervisors intervened in early 2016, and in March 2016, the King's College Hospital R&D office eventually responded to our inquiries with the following decision: "We have reached the following outcome - your study comes under the remit of the Research Governance Framework for Health and Social Care and as such it requires NHS permission before the study can start recruiting participants in the NHS. The [Clinical Research Facility] is hosted by KCH and provides services to KCH and SLaM - the responsibility for the study review is therefore shared between these two organizations for studies undertaken by their staff recruiting their patients or healthy volunteers."

This decision not only meant that co-sponsorship between King's College London and either the SLaM or King's College Hospital NHS Trusts was now required, but also that the existing MHRA and NRES approvals of the buccal naloxone pilot were no longer valid and had to undergo major amendments to allow for the required change in study sponsor. Complicating the issue further, the decision coincided with a procedural change: In March 2016, Health Research Authority (HRA) approval became the centralized process for all research studies involving NHS sites (HRA, 2016), and a backlog of approximately three months was anticipated at HRA-level for the processing of new applications.

Following receipt of the King's College Hospital R&D response, my first supervisor and I decided not to pursue the buccal naloxone pilot further, as the application to the HRA and MHRA for renewed regulatory approval would have delayed the study beyond my PhD submission deadline. The end-of-trial forms were submitted to the MHRA and research ethics committee in July 2016.

While this experience was very frustrating, the buccal naloxone pilot became the case that settled the debate between the IoPPN and KCH R&D offices over the status healthy volunteer studies at the Clinical Research Facility, and the sponsorship issues that caused the delays and failure of the pilot will hopefully not affect future trials.

9.5.3 Can academia-led innovation compete with industry?

As discussed in Chapter 8, I had the opportunity to undertake a student industry placement with the Cambridge-based pharmaceutical company Mundipharma Research Limited from October to December 2016. The central task of my placement was to conduct the data analysis of their recent Phase-I pharmacokinetics trial of concentrated nasal naloxone formulations (1mg, 2mg, 4mg), but I was involved in various other aspects of the naloxone project, including the regulatory submission to the European Medicines Agency (EMA) and marketing considerations.

The placement allowed me to gain a basic understanding of the different steps involved in getting a new pharmaceutical drug from the drawing board to the market. Moreover, it introduced me to the industrial workflow within a pharmaceutical company where every staff member has a clearly defined role with specific competencies. Staff members would apply their specific expertise to any new project for any clinical indication. Tasks that require additional competencies are outsourced. This high-powered staffing model is different from the topic-driven model of clinical academia, where research grants typically fund a

comparatively small number of people to work on a wide range of tasks related to one specific clinical indication.

The contrast between the timelines for the Mundipharma nasal naloxone trial and the buccal naloxone pilot at King's was striking: In August 2015, Mundipharma created the study protocol for its nasal naloxone trial with input from my first supervisor and me. Data collection began in early 2016, and the last patient last visit occurred in late April 2016. Mundipharma thus easily overtook the buccal naloxone pilot. By April 2016, my supervisors and I had been trying for 13 months, in vain, to obtain internal approval within King's Health Partners to start recruitment, after NRES approval had already been secured in March 2015.

This begs the question as to how academia-led innovation can possibly compete with pharmaceutical industry, where, as the Mundipharma nasal naloxone trial illustrates, a CTIMP can be designed, rolled out, and completed in less than a year.

The two planned buccal naloxone studies certainly would have benefitted from dedicated project funding. From my experience, King's Health Partners appears to be moving increasingly towards a commercial business model, but without the benefit of large-scale pharmaceutical industry funding. For instance, the privatization of certain NHS services means that previously existing research capacity is now operating on a fee-for-service basis. Such was the case with the laboratory within the Department of Clinical Biochemistry at King's College Hospital. While research staff at the laboratory were project partners and willing to contribute blood analyses in kind, the laboratory had been privatized, which meant that it was now a separate legal entity, and quotes and service-level agreements had to be arranged for the buccal naloxone trials.

Stronger funding mechanisms may be needed for early-stage translational research. As part of my PhD, I sought additional project support via two funding schemes, the BRC (Biomedical Research Centre) Experimental Medicine and Early Phase Clinical Trials Pilot funding in December 2014 and the BRC STEM *(*Science, Technology, Engineering and Mathematics*)* Early Career Award in January 2016. However, the buccal naloxone project was not considered competitive due to the lack of proof-of-concept pilot data. This put the project in a catch-22: without pilot data from human bloods, the project could not attract funding, and without funding, the project could not collect human bloods.

Following the early termination of the buccal naloxone pilot in July 2016 (see above), my first supervisor approached pharmaceutical industry about taking on the buccal naloxone tablet and conducting the Phase-I trials on behalf of King's College London. However, the pharmaceutical companies did not consider the buccal naloxone tablet financially viable, as

it offered no financial benefit over the intranasal naloxone formulations which were already being explored.

Additional funding schemes may be needed to support the development of therapeutic agents which are not necessarily financially profitable but have potential to address public health issues. This would be particularly relevant for public health in low and middle-income countries with limited financial resources.

9.6 Conclusion

It is disappointing that I was not able to advance the novel instant-dissolving buccal naloxone tablet to in vivo testing during the three years of my PhD studies. The rapidly dissolving tablet was successfully produced to good manufacturing practice standards. The composition, based on three excipients, mannitol, gelatin and sodium bicarbonate, fulfills the design aims for a buccal naloxone tablet for opioid overdose reversal. The buccal naloxone tablets are chemically and physically stable for at least nine months and are suitable for first-in-human proof-of-concept testing to determine the pharmacokinetics of naloxone administration via the buccal route. For the reasons outlined above, naloxone exposure from the buccal tablet has yet to be assessed in humans. If buccal naloxone administration produces acceptable bioavailability, then future work may also investigate ways to optimize the buccal tablet and change its speed of absorption and duration of action, for instance through addition of absorption enhancers and surfactants or modification of pH (.power of Hydrogen).

The concept of buccal naloxone is promising: Tablets generally have greater stability than solutions, and the buccal naloxone tablet is easy to transport, which may provide distinct advantages over injectable and intranasal naloxone formulations. If successful, the buccal naloxone tablet could become a viable, cost-effective alternative to existing products.

In the following and final Chapter 10, I discuss the implications of the integrated findings from this chapter and preceding Chapters 2 to 8 for clinical practice, policy, and future research.

Chapter 10 Discussion

Preface

This final chapter follows the structure of the Discussion sections of the preceding chapters. I first highlight the key findings of the thesis and then discuss its strengths and limitations as well as its implications for clinical practice, policy, and future research.

10.1 What this research adds: Statement of principal findings

Naloxone is a life-saving medication. As described in **Chapter 1**, the antidote is more powerful than its predecessors, while posing fewer side effects and no risk for abuse. In 1996, following nearly three decades of naloxone use in hospital and ambulance settings, a BMJ editorial proposed that pre-provision of naloxone should be made directly available to opioid users for emergency use (Strang et al., 1996).

In **Chapter 2**, I reviewed the evolution of take-home naloxone (McDonald, Campbell, & Strang, in press), finding that – despite positive reception among users, their family members, and the wider harm reduction community – lack of provider familiarity with the intervention challenged early implementation up until the mid-2000s. However, in the past decade, exploration of obstacles and response to social and legal concerns has led to the growth of take-home naloxone programs in number and size. Today take-home naloxone is increasingly accepted as an effective public health strategy.

My Bradford Hill analysis in **Chapter 3** (McDonald & Strang, 2016) was the first systematic review to assess the effectiveness of take-home naloxone in terms of impact on opioid overdose mortality, concluding that – at a low rate of adverse events – take-home naloxone programs reduce overdose mortality among program participants themselves and in the community. In studies with systematic follow-up, 122 out of 123 overdose victims who were administered take-home naloxone survived overdose, while one person died. Taking into consideration that approximately one in every 20-30 heroin overdose events naturally result in death (i.e. equivalent to an expected 4-6 fatalities per 123 overdose events) (Darke et al., 2003), this approximates 3-5 lives saved among the 123 cases of take-home naloxone administration. The US FDA has reported my

systematic review as key evidence for the effectiveness of take-home naloxone (FDA, 2016a).

However, the lack of non-injectable naloxone formulations has impeded widespread take-home provision. In the absence of licensed non-injectable devices, the Massachusetts take-home naloxone program was the first to distribute improvised nasal naloxone kits consisting of a 2mg/ 2mL pre-filled syringe with a nasal mucosal atomizer device in 2005 (Doe-Simkins et al., 2009). These were later introduced elsewhere in the US, Denmark, Norway, and Scotland's Highland region. My review of the evidence base for the off-label nasal spray kits in **Chapter 4** (Strang, McDonald, et al., 2016) outlined how the administration of 2mL of naloxone solution as 1mL per nostril greatly exceeded the volumes that could be absorbed intranasally (i.e. up to 0.2mL per nostril). Moreover, I determined that the existing safety and pharmacokinetic data (i.e. ≤10% bioavailability relative to intramuscular administration, see also Chapter 6) were insufficient to justify the continued off-label use of improvised nasal kits, arguing that medications used in opioid users should be subject to the same testing standards as medications used in any other patient population. Where improvised nasal naloxone kits remain in use, they should thus be replaced with licensed products or, at a minimum, supplemented with a needle for back-up injection in case of non-response to the dilute naloxone nasal spray.

In April 2012, the FDA presented regulatory criteria for non-injectable naloxone products (Hertz, 2012), describing sufficient bioavailability and rapid onset of action relative to the reference treatment of a 0.4mg intramuscular injection as the benchmark. To address the need for formally tested non-injectable naloxone formulations, I conducted a systematic review in **Chapter 5** (Strang, McDonald, Alqurshi, et al., 2016) which applied these regulatory criteria to all 112 FDA-recognized routes of drug administration, concluding that the nasal, sublingual, and buccal routes were potentially suitable for naloxone delivery in an overdose emergency and warranted serious consideration.

Study of the nasal route has been most advanced, and my subsequent review of pharmacokinetic data contained within international patent applications for non-injectable naloxone formulations in **Chapter 6** (McDonald, Glende, Dale, & Strang, in press) identified good bioavailability (i.e. 21-42% relative to intravenous; 26-57% relative to intramuscular administration) for concentrated nasal naloxone spray, with negative association between volume and bioavailability.

In **Chapter 7**, my analysis of previously unpublished data from a 2004 clinical trial established proof-of-concept for IN administration of concentrated naloxone formulations, demonstrating substantial naloxone exposure in the clinically relevant 30 minutes post-dosing (Darke & Duflou, 2016; Tas & McDonald, 2016).

Chapter 8 reports my analysis of the results of a recent Phase-I pharmacokinetic trial of a concentrated nasal naloxone spray that was developed specifically for the indication of opioid overdose reversal and is currently under regulatory review by the European Medicines Agency. My data analysis (McDonald et al., under review) finds equal early naloxone exposure (i.e. within the first 10 minutes post-dosing) from a 2mg/0.1mL intranasal dose and a 0.4mg intramuscular dose – thus meeting the central aim of my PhD project, namely to identify a non-injectable formulation comparable to the intramuscular reference.

Chapter 9 describes my involvement in the development and testing of a novel buccal naloxone tablet (Alqurshi et al., 2016) on which King's College London has applied to register intellectual property, naming me as co-inventor (see Appendix C). Relative to concentrated nasal naloxone sprays, the buccal tablet may have a different pharmacokinetic profile and may be easier to carry due to its smaller size. While the buccal naloxone tablet shows promising in-vitro properties regarding stability and dissolution, pharmacokinetic testing of the tablet in healthy volunteers, which was originally a component of my PhD project, could not be completed within the period of my PhD studies due to regulatory challenges.

Taken together, the findings of my six first-authored papers (plus one first-authored manuscript currently under review) which are incorporated into this thesis strengthen the evidence base for take-home naloxone in general (McDonald, Campbell, et al., in press; McDonald & Strang, 2016) and, more specifically, for the distribution of licensed concentrated nasal naloxone spray for the community-based prevention of opioid overdose deaths (McDonald, Glende, et al., in press; Mundin, McDonald, et al., 2017; Strang, McDonald, Alqurshi, et al., 2016; Strang, McDonald, et al., 2016). The findings of my thesis have several implications for clinical practice and policy, which I discuss in the following sections.

From a methods perspective, this thesis introduces a new exploratory pharmacokinetic parameter to the literature: T50%, defined as the time taken to reach 50% of the peak plasma concentration (Cmax). I first proposed the parameter in Chapter 4 (and later

applied it to the pharmacokinetic data analysis in Chapters 7 and 8) to correct the missing capture of the early curve shape by simple measure of bioavailability (F%), Cmax, and Tmax. Whereas Cmax and Tmax denote the time and extent of the peak concentration, bioavailability relates only to the naloxone proportion that reaches the systematic circulation, neglecting the pace of absorption (Rang et al., 2012). T50% can thus give an indication of meaningful early naloxone exposure between different formulations and routes of administrations. The new parameter has already been adopted by Norwegian colleagues in their recent naloxone paper (Tylleskar et al., 2017) and may also be of value for the pharmacokinetic analysis of other life-saving emergency medications where early absorption is essential.

10.2 Strengths and weaknesses of the thesis

The main strength of the thesis lies in its integration of novel and archived data from academia and industry to create what is likely the most comprehensive work to date on non-injectable naloxone formulations for the prevention for opioid overdose deaths. However, there are at least three major limitations which will need to be addressed in the future.

Limitation 1: Weak evidence base for take-home naloxone distribution

The evidence base from observational studies of take-home naloxone distribution is of moderate to low quality, and the strength of the conclusions of the Bradford Hill systematic review in Chapter 3 is limited accordingly. Of the 22 studies included in the systematic review, none involved randomization. Most studies were uncontrolled and relied on self-report of naloxone usage and overdose outcomes. The number of (self-reported) overdose reversals was used as proxy for the impact of take-home naloxone provision on opioid overdose mortality. However, given that 21 of the 22 studies did not validate self-reported overdose events (e.g. using ambulance records) and follow-up rates differed greatly across studies, this outcome measure must be considered subject to potential bias.

The utility of application of the Bradford Hill criteria (or "considerations") to assess causality has been questioned in the literature. This criticism has been considered in the wider scientific field but appears not to have been considered in the addictions field. For instance, it has been argued, elsewhere, that Hill did not provide a clear definition of what he meant by "causal effect" (Hoefler, 2005). Rothman and Greenland (2005) point out that only the temporality criterion is inarguable and state that use of the criteria as checklist for causation should be avoided as its interpretation is prone to researcher bias. The authors conclude that objective causal criteria do not exist in epidemiology: *"Causal inference in epidemiology is better viewed as an exercise in measurement of an effect rather than as criterion-guided process for deciding whether an effect is present or not".*

Further research is thus likely needed to assess the effect of take-home naloxone distribution on population-wide opioid overdose mortality and to determine what naloxone coverage rates are required. Such future findings may impact confidence in the conclusions of the Bradford Hill systematic review presented in Chapter 3. The need for evaluation of population-wide impact is illustrated by the example of the Scottish National Naloxone Program, where take-home naloxone distribution has been associated with a reduction in the proportion of opioid-related deaths in the first four weeks following prison release (Bird et al., 2015, 2016), but this reduction in deaths in the high-risk population of prisoners on release has not translated to the wider population of opioid users. Despite widespread take-home naloxone provision, the largest number of drug-related deaths on record was registered for 2016 (i.e. 867 deaths, of which 88% opioid-related), representing a greater than hundred percent increase since 2006 (NRS, 2017). There are clearly still aspects of the observed data which need more probing study.

In 2014, the World Health Organization Guideline Development Group issued the recommendation that "people likely to witness an opioid overdose should have access to naloxone". Interestingly, the Guideline Development Group determined that – despite the low-quality evidence from existing observational studies – this recommendation should be strong due to the risk-benefit ratio of naloxone distribution, i.e. the potentially life-saving nature of the intervention and the apparent absence of significant harm. In light of this recommendation, it seems unlikely (for most settings) that parallel trial designs, where a control group is not provided access to take-home naloxone, would be considered ethical.

Cohort studies and database linkage studies (e.g. tracking individuals who have or have not been prescribed naloxone in mortality databases) are feasible but would require large sample sizes. It also needs to be borne in mind, in the analyses and interpretations, that the emerging evidence can be confounded by the possibility that take-home naloxone recipients may use their naloxone supply to reverse overdose in a third person.

A more sophisticated approach which would allow for evaluation of impact on opioid mortality rates involves the stepped wedge randomized design (Brown & Lilford, 2006), where take-home naloxone distribution is rolled out sequentially across all participating clusters (e.g. cities or regions) over multiple time-points, and the order of intervention delivery across sites is randomized. A key feature is that once a cluster begins to receive the intervention, it does not switch back to the control. A stepped wedge design requires that the intervention is not available in any of the participating clusters at baseline to allow for comparison of outcomes (i.e. mortality rates) before (i.e. control) and during exposure to the intervention. There may be special opportunities, available for only a short period of time, as the provision of take-home naloxone is gradually being accepted as an expected or required practice. For example, countries such as Sweden, which have robust data collection on drug-related deaths and are only now considering the introduction of take-home naloxone thus have the opportunity to strengthen the evidence base by using a stepped wedge randomized design for evaluation.

Limitation 2: Lack of human in vivo data for buccal naloxone

For the reasons discussed in Chapter 9, I was unable to conduct two planned clinical trials (EudraCT numbers: 2014-001802-16, 2016-000582-23) of the pharmacokinetics of buccal naloxone in healthy volunteers. Even though the buccal naloxone tablet has been manufactured and is fit for first-in-human testing, its bioavailability can at present only be estimated based on preclinical data (see Chapter 5). It is hoped that future completion of the Phase-I trial of the buccal tablet will fill this knowledge gap and allow the tablet to advance to the next stages of drug development – and potentially to regulatory approval. The time series for blood sampling in the trial protocols in Chapters 8 and 9 is identical, meaning that the results of the buccal naloxone tablet trial, once completed, will allow for direct comparison of its pharmacokinetics to those of the 1mg/0.1mlL, 2mg/0.1mL, and 4mg/0.2mL nasal spray formulations.

Limitation 3: Lack of pharmacokinetic data from clinical samples

The third limitation concerns the fact that all pharmacokinetic data reported in this thesis, and indeed all pharmacokinetic studies of nasal naloxone conducted internationally, have thus far only been collected in healthy volunteers, and the degree of potential variation in clinical samples has yet to be determined. Pharmacokinetic data are sample-dependent and describe aggregate blood plasma concentrations of a specific formulation administered to an individual on a given occasion (Rang et al., 2012). The bioavailability of a naloxone formulation is thus not solely a function of the formulation itself but is also affected by intra-subject and inter-subject variability. Cross-over designs, as used in the studies in Chapters 7 and 8, seek to reduce these sources of variability (MacKenzie, 2013), and the similarity of the bioavailability and Tmax values in Chapter 8 and the studies by Krieter et al. (2016) and Tylleskar et al. (2017) support the validity of these findings. Nonetheless, it needs to be borne in mind that the registration trials reported in Chapter 8 and by Krieter et al. (2016) tested the pharmacokinetics of intranasal naloxone under optimal laboratory conditions in healthy volunteers who underwent extensive screening and frequent nasal passageway examinations. The bioavailability of intranasal naloxone in patients with nasal or hepatic irregularities may thus differ substantially (see Chapter 8). Similarly, while the healthy volunteer studies in Chapters 7 and 8 and those by Krieter et al. (2016) and Tylleskar et al. (2017) support good tolerability of the concentrated intranasal formulations, no definite conclusions can be drawn as to their clinical safety in the target population of opioid overdose victims.

What kind of studies could strengthen the pharmacokinetic evidence and prepare for clinical trials?

At least three kinds of studies could be conducted to strengthen the pharmacokinetic evidence for concentrated nasal naloxone spray and prepare for clinical trials in the target population.

Firstly, the generalizability of the pharmacokinetic evidence could be increased by conducting a richly sampled Phase I pharmacokinetic study with the aim to study the sources and correlates of variability in naloxone concentrations between individuals. While pharmacokinetic study of naloxone in opioid users would undoubtedly be ethically challenging, non-opioid using subjects with features similar to the target population could

be recruited instead. Dose-concentration relationships can be affected by subjects' demographical and clinical features, such as body weight, metabolic and excretory functions, and the presence of other substances (FDA, 1999). There may thus be merit in studying the variability of naloxone concentrations in non-opioid using individuals with nasal abnormalities or nasal mucosal damage, varying degrees of hepatic impairment, very low or high body weight (or Body Mass Index, BMI), and in smokers – all of which were exclusion criteria for the studies in Chapters 7 and 8. For instance, it is currently unknown whether nasal damage from drug snorting would decrease (due to scarring) or increase (due to greater mucosal permeability) the absorption of nasal naloxone. This could potentially be tested in (former) cocaine users with nasal damage.

Secondly, in order to empirically test the simulations of repeat administrations presented in Chapter 8, the effects of repeat dosing (administering a naloxone nasal dose every 3 minutes, for instance) on naloxone plasma concentrations could be assessed in healthy volunteers and compared to parenteral routes. This could also involve comparison of repeat administration of the nasal spray in the same nostril versus the alternate nostril. Such study of repeat administration could inform the development of treatment algorithms for naloxone nasal spray, which currently do not exist.

A third option involves existing clinical situations which provide the opportunity to safely study the efficacy of naloxone nasal spray and required dosage in controlled medical settings. These clinical situations include naloxone reversal of opioid anesthesia following surgery as well as opioid overdose reversal in ambulance settings or in supervised injecting facilities. The post-operative recovery setting may provide the added benefit that patient consent can be obtained prior to surgery. Where consent is given, blood samples for pharmacokinetic analysis could thus be drawn during opioid anesthesia and naloxone reversal and provide valuable information on how naloxone blood levels correlate with recovery. Existing research plans for an ambulance-based trial comparing intranasal and intramuscular naloxone are described in more detail in Section 10.5.2

What statistical tests could be used to test a hypothesis of "equivalence" between naloxone preparations compared to "gold standard"/ treatment as usual?

With regard to statistical tests, the standard approach to test for pharmacokinetic equivalence (i.e. equivalence of the plasma concentration profiles) is to perform a bioequivalence evaluation. (Bioequivalence testing involves calculating comparison ratios for a test treatment and a reference treatment for AUC and Cmax, plus associated confidence intervals. If the 90% confidence intervals for the comparison ratio (test/reference treatment) fall within the range of 80 to 125%, bioequivalence can be concluded).

However, pharmacokinetic bioequivalence is only relevant if two treatments are given by the same route of administration (e.g. two treatments for oral administration). For the comparison of one or multiple naloxone nasal spray formulations to the clinical standard of an intramuscular injection, bioequivalence evaluation thus does not apply.

Repeated measures ANOVA can be applied to compare PK parameters (e.g. Cmax, AUC) from different routes of administration. For 2×2 crossover designs (e.g. one intranasal dose vs. one intramuscular reference dose), a standard repeated measures ANOVA can be conducted with sequence as between factor and treatment as within factor.

For crossover designs that are more complex than the 2×2 crossover (such as the trials in Chapters 7 and 8 which compared multiple nasal spray doses), extensive modeling is often required, and mixed-effects linear models may be considered preferable, as they can deal with missing values and account for potential sequence, period, and carryover effects (Li, 2014; see also Senn, 2002).

10.3 Possible mechanisms and implications for clinicians

Multiple products are currently under review by the European Medicines Agency, and a first concentrated naloxone nasal spray will likely receive regulatory approval from the European Medicines Agency in late 2017 or early 2018.

10.3.1 Implications for take-home naloxone provision

Injectable naloxone formulations have been considered a barrier to community-based naloxone use (Beletsky et al., 2012; Wermeling, 2013) on the basis that bystanders may be less willing to administer an injection for lack of familiarity with needle-and-syringe assembly or for fear of needle-stick injury and potential contraction of blood-borne diseases (e.g. hepatitis C, HIV) which are highly prevalent among injecting drug users (Degenhardt et al., 2016). A licensed naloxone nasal spray would remove these barriers and may have several implementation advantages.

Since a nasal spray does not require training in needle-and-syringe assembly, it could be pre-provided to a wider intervention workforce, including hostel staff, outreach workers, and police. In fact, the London Metropolitan Police has already expressed interest in carrying naloxone once a licensed nasal spray becomes available in the UK (Broughton, 2017).

Moreover, by removing the needle from the antidote, non-injectable naloxone could also be made available in communities (e.g. Liverpool) and countries (e.g. Sweden) which thus far have blocked take-home naloxone implementation on the basis that the administration of injections is restricted to medical professionals (EMCDDA, 2016a).

Clinicians may also feel more comfortable about providing a naloxone nasal spray to opioid users and their family members. Injecting drug users have expressed strong preference of intranasal naloxone over injection-based administration, among others because a nasal spray would eliminate the need to carry a spare clean needle and would be less alarming to use in public (Kerr, Dietze, Kelly, & Jolley, 2008). Family members and other potential overdose witnesses without medical training may prefer the functionality of the ready-to-use Aptar device compared to existing pre-filled syringes which require manipulation (UKMi, 2016) and to improvised nasal kits (see Chapter 4) for which cases of assembly failure have been reported (Doe-Simkins et al., 2009). Family members already carry out 20% of overdose reversals (Bagley, Forman, Ruiz, Cranston, & Walley, 2017), and this proportion could increase in future with ready-to-use non-injectable devices.

The ease of administration of the Aptar device may also be advantageous when those witnessing an overdose are heavily intoxicated themselves. Such was the case in a London-based audit study of drug overdose deaths (n=148) investigated by coroners in

2003 (Hickman et al., 2007). The coronial files suggested that even though 60% of overdoses were witnessed, the witnesses' capacity was compromised in most cases. The authors estimate that one quarter of witnessed deaths could have been prevented had the witnesses intervened sooner. (*Nota bene:* It is unclear if any of the witnesses had access to take-home naloxone, which had only been introduced by very few services in South London in the year 2001, see Chapter 2).

This points to an issue that availability of non-injectable naloxone products alone is unlikely to solve. Take-home naloxone administration is only possible where death is not immediate and a witness is present who recognizes the opioid overdose. Using alone is a known risk factor for fatal overdose and may particularly affect older opioid users (age ≥40 years) (EMCDDA, 2016a, 2016b; Hickman et al., 2007); whose overdose risk is already pronounced due to physical comorbidities and who may be more likely than younger cohorts to live alone.

Particularly for those who inject alone, mechanisms for detection of opioid overdose are urgently needed. Survival rates of overdose could potentially be improved through novel technology that would detect when a user is unresponsive, trigger an ambulance call, and submit the GPS location of the overdose victim (Tas & McDonald, 2016). However, despite commendable efforts by the US Substance Abuse and Mental Health Services Administration (SAMHSA) to promote the development of technology-based tools for opioid overdose prevention (3), these remain largely non-existent.

In their audit of drug overdose fatalities, Hickman and colleagues (2007) found that over a third of cases (36%) had been in contact with specialist drug treatment services, emergency care (ED visits) or primary care in the month prior to their death. While drug treatment services may be the obvious access point for take-home naloxone provision due to the high concentration of opioid users, this finding suggests that primary care and emergency care are also potentially useful venues for engaging the high-risk subpopulation of users not enrolled in opioid substitution treatment (Degenhardt et al., 2011; Pierce et al., 2016). The implications of my thesis for take-home naloxone provision across these three settings are considered in the following sections.

10.3.2 Drug treatment services

A recent cost-effectiveness modelling study (Uyei, Fiellin, Buchelli, Rodriguez-Santana, & Braithwaite, 2017) suggests that the provision of take-home naloxone in combination with methadone treatment is cost-saving. This extends the findings of two earlier cost-effectiveness modelling studies (Coffin & Sullivan, 2013a, 2013b) who concluded that take-home naloxone was cost-effective even under conservative model assumptions and lends further support to the large evidence-base for opioid substitution treatment. Multiple systematic reviews and meta-analyses show that retention in opioid substitution treatment reduces heroin use and protects against overdose mortality (Degenhardt et al., 2011; Mattick, Breen, Kimber, & Davoli, 2009; Sordo et al., 2017).

Studies in Italy (Davoli, Bargagli, Perucci, Schifano, Belleudi, Hickman, Salamina, Diecidue, Vigna-Taglianti, et al., 2007), England (Cornish et al., 2010), Norway (Ravndal & Amundsen, 2010) and Scotland (Merrall, Bird, & Hutchinson, 2013) have found that the first month following the end of treatment generally bears an elevated risk of overdose (see also Chapter 2). Take-home naloxone should thus be a standard of care for patients in opioid substitution treatment as well as those in abstinence-based treatment. Strang and colleagues (2003) found that patients who had successfully completed inpatient abstinence-based treatment for opioid use disorder were more likely to die of overdose than those who had failed to complete the program. Abstinence-based treatment providers have traditionally been reluctant to distribute take-home naloxone (McDonald et al., 2016), presumably for fear of a safety net effect – for which no empirical evidence exists (Kerensky & Walley, 2017; McDonald & Strang, 2016). However, availability of a licensed naloxone nasal spray (or other non-injectable formulations) may facilitate organizational buy-in from clinical leadership, as the nasal route of administration bears no resemblance to injecting drug use and would unlikely be considered to trigger relapse.

10.3.3 Primary care

Despite evidence of reduced mortality risk following primary care-based initiation of opioid substitution treatment (Kimber et al., 2010) and despite extensive contact with users seeking treatment for often complex health issues, many primary care providers fail to meet their central role of coordinating care for opioid users (Robertson, 2016).

While some primary care providers have expressed favorable attitudes towards wider naloxone availability in survey studies, many have remained wary of providing take-home naloxone (Barry, Klimas, Tobin, Egan, & Bury, 2017; NPHL, 2014). US primary care providers described insufficient time during patient appointments and inability to follow up with patients as main organizational barriers to take-home naloxone (Binswanger et al., 2015). Canadian primary care providers considered existing naloxone guidelines inadequate and identified the lack of user-friendly naloxone devices, sufficient funding and training as central barriers to take-home naloxone provision (Leece, Orkin, Shahin, & Steele, 2015). In Scotland, many primary care providers reported low awareness of the national take-home naloxone program, which points to the need for provider training (Matheson et al., 2014). These implementation barriers also highlight the need to change policy and allocate appropriate funding to prioritize the management of opioid users in primary care, including take-home naloxone provision (Robertson, 2016).

Take-home naloxone research has been largely confined to injecting drug users, and the question of co-prescription of naloxone as a universal precaution for chronic pain patients being treated with opioids in primary care is just now being raised (Kerensky & Walley, 2017). A San Francisco-based project of naloxone co-prescribing for primary care patients receiving long-term opioid pain therapy established that the intervention was feasible, acceptable to patients (Behar, Rowe, Santos, Murphy, & Coffin, 2016) and associated with significantly reduced opioid-related emergency department (ED) visits at 1-year follow-up (Coffin et al., 2016). Naloxone nasal spray may be more acceptable to chronic pain patients than an injectable kit, since these patients may not consider themselves at risk of overdose and may not want to be associated with injecting drug use in the broadest sense.

10.3.4 Emergency care

Emergency care settings present the unique opportunity to reach high-risk patients seeking treatment for opioid-related injuries and overdose. The Massachusetts take-home naloxone program already provides take-home naloxone at EDs, and feasibility has recently also been studied elsewhere. A British Columbia survey of ED patients at risk of opioid overdose (Kestler et al., 2017) found that two-thirds accepted take-home naloxone kits when offered to them at the ED, highlighting the potential of this setting for

overdose prevention. Ambulance-based take-home naloxone provision following overdose reversal is currently being piloted in San Francisco, and the feasibility of using the post-resuscitation period as a “teachable moment” for brief intervention – similar to the Screening, Brief Intervention, and Referral to Treatment (SBIRT) model (Babor et al., 2007; Barbosa, Cowell, Bray, & Aldridge, 2015; Madras et al., 2009) – is now being explored.

10.3.5 Dosing

The approval of one or multiple concentrated naloxone nasal spray products by the European Medicines Agency would significantly diversify the range of naloxone formulations available to clinicians. If either product receives regulatory approval, the pharmacokinetic data reported in this thesis for the 2mg/0.1mL nasal spray as well as the data previously published by Krieter et al. (2016) on the Adapt 4mg/0.1mL spray should be made available to clinicians so that they can make correct clinical decisions on dose adjustment for the new nasal spray (relative to the established injectable formulations for which dose guidance has been developed).

The 2mg/0.1mL intranasal dose tested in Chapter 8 was characterized by maintenance of substantial plasma levels for two hours post-dosing. The concentrated nasal spray formulations tested by Krieter et al. (2016) and Tylleskar et al. (2017) had similar profiles. Concentrated nasal naloxone spray could thus prevent re-narcotization following heroin overdose and be beneficial for the treatment of overdose from long-acting opioids (see Chapter 1)

The dosage of any new intranasal formulation will need to strike a balance between reversing opioid action without causing severe adverse reactions (Hertz, 2012). Reports of the harm caused by naloxone over-antagonism have been described, and high-dose naloxone formulations with increased risk of over-antagonism may also result in negative attitudes from drug users, as previously reported (Neale & Strang, 2015).

It is worth noting that the FDA and the European Medicines Agency appear to differ in their assessment of the safety implications of concentrated naloxone nasal spray formulations. Whereas the FDA has highlighted that the potential benefits of the Adapt NARCAN 4mg/0.1mL product (i.e. overdose reversal) outweigh the risks of withdrawal syndrome (Hertz, 2015). Meanwhile, the European Medicines Agency, in their review of

the 2mg/0.1mL formulation studied in Chapter 8, has raised several questions regarding the potential risks of withdrawal. It is interesting to note that a bold regulatory approach is not uncommon for the FDA: A recent analysis by Downing et al. (2017) found that one in every three new drugs approved by the FDA between 2001 and 2010 has had post-market safety issues.

At a minimum, clinicians will thus need to carefully monitor any licensed new naloxone product for its potential side effects and non-response rate, and take-home naloxone recipients should be actively encouraged to report any adverse reactions or safety issues that may occur.

10.3.6 Potential use for other clinical indications

By removing the needle from naloxone, non-injectable formulations of the opioid antagonist may potentially also be of value for the treatment of other clinical indications, where daily dosing is required. Binge eating disorder, for instance, is associated with mu-opioid receptor dysregulation (Heal et al., 2017; Majuri et al., 2017). According to a recent literature review (McElroy, Guerdjikova, Mori, & Keck, 2015), a conference abstract on a double-blind Phase-II randomized controlled trial sponsored by Lightlake reported a reduction of binge eating episodes and body mass index (BMI) following daily intranasal naloxone treatment (2-4mg; volume not reported) over the course of six months. An upcoming 12-week multi-site clinical trial sponsored by Opiant will assess the impact of daily treatment of up to two doses of the Adapt naloxone nasal spray (4mg/0.1mL) on binge eating episodes in patients with bulimia nervosa. One of the participating study centers is the Eating Disorders Research Group at King's College London, where data collection is scheduled to commence in June 2017 under supervision of Professor Janet Treasure.

10.4 Possible mechanisms and implications for policymakers

10.4.1 Calls for universal take-home naloxone provision

My Bradford Hill analysis in Chapter 3 concluded that take-home naloxone distribution to opioid users should be introduced as standard of care for the community-based prevention of overdose deaths (McDonald & Strang, 2016). To date, only modest

volumes of take-home naloxone kits have been distributed relative to the growing international clinical need, as evident in 106,000 annual deaths from opioid overdose worldwide (UNODC, 2016b).

Beyond lack of funding or political support, low prescriber awareness and commitment persist as central barriers to wider take-home naloxone provision. Despite evidence of effectiveness and endorsements from professional organizations (ACMD, 2000, 2012, 2016; AMA, 2012), many providers fail to integrate take-home naloxone into standard care for at-risk patients. Dissemination was found to be difficult even among addiction treatment staff (Mayet, Manning, Williams, Loaring, & Strang, 2011) with the anticipated cascade of the 'train-the-trainer-model' occurring at the disappointing pace of one drug user trained per clinician trainee in an average of 11 months.

The introduction of non-injectable naloxone alone may not change provider behavior. Providers struggle with competing clinical demands, making opt-in medical services low priority. A more proactive approach whereby take-home naloxone was routinely prescribed to all at-risk patients unless patients declined ('opt-out' system) would likely increase coverage. In theory at least, an 'opt-out' system of required naloxone pre-provision could even open the doors to the possibility of medical malpractice lawsuits in cases where providers issue high-dose opioid scripts without co-prescribing take-home naloxone, and the patient then suffers opioid-related injury or death.

In a recent US study, Barnett and colleagues (2017) conducted a retrospective analysis of prescription claims for Medicare patients (n=377,629; mean age: 69 years) who had an ED visit during the study period (2008-11) and had not been prescribed opioids in the 6 months leading up to the ED visit. The authors found that patients' opioid use in the 12 months following the ED visit was associated with the prescribing behavior of the treating ED physician. The ED physician's opioid prescribing intensity (both in terms of dose and frequency) predicted patients' opioid use at 12 months, with long-term opioid use (≥180 days' opioid supply) significantly higher among patients treated by a high-intensity than a low-intensity prescriber (odds ratio: 1.31; 95% confidence interval = 1.24, 1.39) during their initial ED visit.

Opt-out guidelines for required take-home naloxone provision, together with mandatory provider participation in prescription drug monitoring programs (PDMPs) (Moyo et al., 2017; Wen, Schackman, Aden, & Bao, 2017) could thus lead to substantial improvements in providers' prescribing behavior and protect patients' lives.

With a view to global naloxone access, the United Nations Office on Drugs and Crime (UNODC) proposed an international coverage target at the 60th session of the Commission on Narcotic Drugs in March 2017 (UNODC, 2017), analogous to the existing UNAIDS (Joint United Nations Program on HIV/AIDS) 90-90-90 'test and treat' strategy that had been introduced to help end the AIDS epidemic (UNAIDS, 2014), The UNODC target specifies that '90% of those likely to witness an opioid overdose (users, peers and family) will have received training in overdose risk and emergency management, of whom 90% will have received take-home naloxone, of whom 90% will be carrying naloxone or have it close at hand.' While this target is extremely ambitious in nature and does not define a target date for attainment, the former two aims may represent useful indicators to quantify and monitor overdose prevention efforts and naloxone coverage relative to the target population in countries affected by opioid-related mortality.

Future studies will need to look at the extent to which widespread take-home naloxone coverage, as perhaps achieved in Scotland (Bird, McAuley, Munro, Hutchinson, & Taylor, 2017; McAuley et al., 2017), Norway (Madah-Amiri et al., 2017) and several states in the US (Walley, Xuan, et al., 2013), results in a reduction in opioid overdose mortaliy at the state or national level. Researchers estimate that target naloxone coverage should exceed 100 kits per 100,000 population (Walley, Xuan, et al., 2013) or at least nine times as many naloxone kits as there are annual opioid-related deaths to impact opioid mortality (Bird et al., 2015; Madah-Amiri et al., 2017). However, optimum coverage levels of take-home naloxone will likely be context-dependent. Vickerman and colleagues (2006), using mathematical model projections, sought to determine a coverage threshold for syringe distribution that would lead to reductions in HIV prevalence among injecting drug users, have highlighted the challenges of establishing a single universal coverage target, and they consider that multiple environmental factors would come into play. A recent spatial analysis of San Francisco census tracts indicates that greater geographical distance to take-home naloxone distribution sites was associated with a lower number of naloxone reversals (Rowe et al., 2016). This suggests that required coverage levels may also differ by population density, e.g. for urban versus rural communities. In terms of global health, target naloxone coverage will likely depend on the existing healthcare infrastrure, with increased naloxone coverage needed in countries where access to opioid subsitution treatment and availiability of emergency medical care are low or associated with risk of financial burden or legal consequences for those seeking help.

10.4.2 Over-the-counter naloxone

Injectable medicinal products are subject to prescription according to Article 71 of the European Union Medicinal Products Directive (2001/83) (EMCDDA, 2016a): “Medicinal products shall be subject to medical prescription where they […] are normally prescribed by a doctor to be administered parenterally.” Since naloxone is currently licensed only for injection by the European Medicines Agency, it follows that naloxone should normally be available by prescription. Given that naloxone self-administration is unlikely during overdose, prescription-only status implies that naloxone can be administered to the patient to whom the prescription was issued by only a medical practitioner (e.g. doctor or nurse) or those acting under the medical practitioner’s instructions (e.g. family members) (EMCDDA, 2016a).

By definition, non-injectable naloxone products, including nasal sprays, would not involve parenteral administration and may therefore enable future re-classification to over-the-counter medication (EMCDDA, 2016a). Over-the-counter status already exists in Italy and Australia (notably for injectable naloxone), and Canada, the UK, and several states in the US have put special guidelines in place to make naloxone available without prescription.

Until recently, Italy was the only country where naloxone was available without a prescription. In 1996, the Italian Ministry of Health classified naloxone as an over-the-counter medication, allowing pharmacists to issue naloxone without a prescription (*Senza Obbligo di Prescrizione)* (ForumDroghe, 2016, 2017; Lenton & Hargreaves, 2000; WHO, 2014). However, naloxone cannot be publicly displayed on shelves to which customers have direct access. Customers must request naloxone directly from the pharmacist. While no causal conclusions may be drawn, the 1996 introduction of over-the-counter status in Italy was succeeded by a gradual decline in opioid overdose mortality rates, with 470 deaths in 1999, 280 in 2005, and 101 in 2015 (ForumDroghe, 2016, 2017). As of 2016, 57 Italian harm reduction services distribute take-home naloxone, but there are stark regional disparities, with services predominantly clustered in the major metropolitan areas (i.e. Rome, Milan, Bologna, Turin, Naples) (ForumDroghe, 2016).

Although take-home naloxone was only introduced in Australia in 2011, Australia became the second country to have naloxone formally available over-the-counter, following the decision of the Therapeutic Goods Administration to place “naloxone when

used for the treatment of opioid overdose" on Schedule 3, thereby approving over-the-counter status (Lenton et al., 2016). Since early 2016, Australian community pharmacists have been able to supply naloxone without a prescription.

In Canada, take-home naloxone programs exist in seven of the 13 provinces and territories, with large programs in British Columbia (120 sites, 6,389 kits distributed) and Ontario (22 sites, 2,734 kits distributed) (CCSA, 2016). In 2016, Health Canada approved the previously FDA-licensed nasal naloxone product (NARCAN®; 4mg/0.1mL) and issued an interim order to make the spray available without a prescription (CBCnews, 2016).

Select US pharmacies in at least 15 states have special practice agreements allowing pharmacists to sell naloxone (incl. the FDA-approved nasal spray) without a prescription (EMCDDA, 2016a). However, it is unclear if or how soon formal re-classification of naloxone from prescription-only medicine to over-the-counter status may occur. An earlier legal analysis suggested this regulatory process might be lengthy and cost-intensive (Burris et al., 2001), as the FDA would require additional data demonstrating the ability of laypersons without medical training to correctly diagnose an overdose and administer the formulation (Compton, Volkow, Throckmorton, & Lurie, 2013; FDA, 2012).

In the UK, new UK legislation, as summarized in the 2015 PHE guidelines, allow people engaged or employed in NHS drug treatment services to make take-home naloxone available to opioid users, family members, and hostel staff without prescription, provided the naloxone supply is documented accurately (PHE, 2016). Even though naloxone technically remains a prescription-only medication, the guidelines reduce the staffing burden for take-home naloxone as staff without prescribing authority can issue take-home naloxone for emergency use. Community pharmacists are now being allowed, according to the new UK legislation, to provide naloxone directly to opioid users.

While over-the-counter status would likely reduce bureaucratic hurdles, naloxone access solely over-the-counter, i.e. without additional free distribution, may only yield limited community-based coverage (Pricolo & Nielsen, 2017). Such is the case in Italy, where some regions remain without community-based naloxone coverage despite over-the-counter status, presumably because of lack of a national harm reduction policy and insufficient public investment (ForumDroghe, 2016). As follows, the Italian experience highlights that over-the-counter status *per se* does not imply necessarily that pharmacies will stock naloxone.

10.4.3 Cost of non-injectable naloxone formulations

The issue of take-home naloxone cost also needs to be considered. In countries where individuals can purchase naloxone, it remains unknown how likely potential overdose witnesses are to access and obtain naloxone via take-home naloxone programs at no cost versus over-the-counter medication for sale. By analogy, in the prevention of sexually transmitted infections (STIs), a systematic review identified cost as barrier to condom use (Ubrihien, Davies, & Driscoll, 2016). Consequently, recent National Institute for Health and Care Excellence (NICE) guidelines recommend free-of-charge condom distribution schemes to target populations at highest risk of STIs (Iacobucci, 2017; NICE, 2017). A dual implementation model is therefore recommended: potential over-the-counter sales of non-injectable naloxone must not replace free-of-charge distribution schemes in future.

When comparing the different existing naloxone devices, with ampoules being the most basic, there is a clear trade-off between usability and cost. This point is perhaps best illustrated with the example of the Kaléo Pharma's naloxone auto-injector (Evzio®; 0.4mg/0.4mL), which was FDA-approved in April 2014 (Kaleo, 2014). The product, which is packaged with two single-use auto-injectors and a trainer (FDA, 2016), does not require any assembly and provides audio-instructions. However, its usability comes with a hefty price-tag: At US $4,500 (Lazarus, 2017), the auto-injector becomes almost irrelevant for community-wide provision.

The affordability of non-injectable naloxone products will define their availability in a healthcare system, and ultimately, their accessibility for the target population. The different manufacturers of the naloxone nasal sprays currently under review by the European Medicines Agency have indicated that they would aim to introduce their respective products (packaged with two single-use devices) at a market price that would match that of the Prenoxad® pre-filled syringe, which is currently listed in the BNF at £15.30 (NHS indicative price) (BNF, 2017).

Bearing in mind that affordability will likely differ by country and depend on the purchasing power of its healthcare system, the question of cost of non-injectable naloxone becomes particularly relevant for global health. Following my involvement in the development of the 2014 WHO Guidelines (WHO, 2014), I have recently had the opportunity to support UNODC as a consultant working on a feasibility study of take-home naloxone provision, including potential use of intranasal naloxone, in low- and

middle-income countries (LMIC) in Eastern Europe and Central Asia. With support from the Global Fund, the four project countries currently procure naloxone ampoules from two manufacturers in Ukraine and Poland at the low cost of approximately US $0.50 per ampoule (0.4mg/ml), subject to exchange rate. Local non-governmental organizations typically hand out two take-home ampoules per client, i.e. equivalent to a total medicine cost of US $1.00 per person. Given the current cost disparity between the nasal spray and local ampoule supply, the purchase of naloxone nasal spray is not sustainable for the project countries at present. Whether non-injectable products can improve community-based naloxone availability in LMIC in the future remains to be seen. Bulk-buying and the production of generics could lower costs in the long term, as has been achieved for second-line antiretroviral therapy for HIV/AIDS in LMIC, where the medication cost per patient per year was reduced by 60% from US $1,500 in 2006 to US $527 in 2011 (Unitaid, 2016).

10.5 Questions for future research

Many questions are still unanswered about take-home naloxone in general and non-injectable naloxone in particular, including questions about efficacy and optimal dose range (especially for overdose from synthetic opioids) (FDA, 2016a), and questions on implementation strategies, user engagement, and device preference. I have sought to address these questions in the following sections.

10.5.1 Clinical experimental studies: Ambulance-based

While the pharmacokinetic studies in healthy volunteers in Chapters 6 to 8 have allowed me to compare naloxone exposure from different routes of administrations and formulations, pharmacokinetic data only provide estimates of expected performance in clinical samples (see Chapter 8). It is thus crucial to examine the efficacy of concentrated naloxone nasal spray versus intramuscular naloxone in the target population of opioid overdose victims. Given the life-threatening nature of opioid overdose, this cannot safely and ethically be tested in a non-medical setting. The ambulance setting is crucial for patient safety and has full supplementary interventions available, if required. Two ambulance-based Australian randomized trials (Kelly et al., 2005; Kerr et al., 2009) have

previously successfully tested intranasal (2mg) versus intramuscular (2mg) naloxone for treatment of opioid overdose. However, the findings of these trials are outdated because dilute naloxone nasal spray formulations (2mg/mL; 2mg/5mL) were used. Ambulance-based study of the efficacy of concentrated naloxone nasal spray (e.g. 2mg/0.1mL) for take-home naloxone use is thus urgently needed and would allow for robust testing of its non-response rate, dose adequacy and inter-subject dose variability, and the speed with which concentrated naloxone nasal spray reverses central opioid action.

Together with my PhD supervisor Professor Sir John Strang, I am currently developing a feasibility trial that will assess the acceptability and logistics of conducting a randomized controlled trial of intranasal versus intramuscular naloxone in the London Ambulance Service. London Ambulance Service staff has already expressed preliminary interest in trialing concentrated naloxone nasal spray, as it could remove the risk of needle-stick injury and thus improve occupational health for paramedics (Barton et al., 2005; Barton et al., 2002; Merlin et al., 2010; Robertson et al., 2009). The feasibility study will explore paramedics' attitudes towards the use of naloxone nasal spray in clinical practice and towards participation in a randomized trial and will also assess the case notes of a small number of opioid overdose victims (n=50) for completeness regarding key clinical outcomes. A key limitation of the Australian trials was that their open-label design confounded a key outcome (use of rescue naloxone by intramuscular injection) in that it was not clear whether the use of a rescue injection was a true reflection of the lack of efficacy of the dilute naloxone nasal spray or the paramedics' expectation thereof. A double-blind, double-dummy design will therefore be considered as part of the feasibility study.

10.5.2 Clinical experimental studies: Laboratory setting

While an ambulance-based randomized controlled trial would provide valuable evidence on intranasal naloxone efficacy and dose comparability in clinical samples, its central limitation concerns the fact that, apart from perhaps the duration of action of the opioid agonist and the presence of absence of alcohol intoxication, it is difficult to determine what opioids were consumed in what quantities and what other concomitant drugs may have been involved in the overdose.

Studies of fatal (Hickman et al., 2007) and non-fatal (Darke, Ross, & Hall, 1996) opioid overdoses have reported that approximately two thirds of heroin overdoses occur in the presence of other central nervous system depressants, i.e. most frequently alcohol, but also cocaine, benzodiazepines, and other opioids. The issue of polysubstance use has recently received considerable attention in the context of rising rates of overdoses involving fentanyl and fentanyl derivatives in North America (FDA, 2016; Kerensky & Walley, 2017; Paone & Kunins, 2016; Rudd, Seth, David, & Scholl, 2016). However, it is largely unknown how the presence of multiple central nervous system depressants may impact the chances of overdose survival, both in terms of how their pharmacological interaction may affect tolerance levels and in terms of the naloxone dosage levels required to reverse such overdoses. Two methodological approaches involving laboratory-based testing may shed light onto this issue and are not mutually exclusive.

In a "For Debate" piece in *Addiction*, Hickman et al. (2008) have proposed the integration of epidemiological data and findings from preclinical experiments. This translational approach would offer the opportunity to use animal models to experimentally test the interaction between commonly used opioid agonists and other central nervous system depressants at different dose levels and in the presence or absence of naloxone. A recent multidisciplinary study by Lyndon et al. (2017) has integrated evidence from 1) a preclinical experiment in mice which measured the effects of [pregabalin] versus [pregabalin + morphine] treatment on respiratory depression with 2) Office for National Statistics (ONS) data, 3) community prescriptions data, and 4) qualitative interview data, finding that co-use of gabapentin or pregabalin can increase the risk of fatal opioid overdose in heroin users through interaction or additive effects on respiratory depression.

While this innovative approach is extremely promising, a limitation may be that it is unclear to what extent pharmacokinetic and pharmacodynamics data truly "translate" across species. Differences in protein binding are common between human plasma and rodent plasma and can have large impact on free drug metabolite concentrations and drug effect (Rang et al., 2012).

The second methodological approach thus involves the possibility of studying the pharmacodynamics of naloxone directly in opioid users. In theory at least, two study designs come to mind which could be used to test the potency of naloxone relative to different opioid agonist drugs. The first design could test the antagonizing effects of a

standard naloxone pre-treatment (e.g. 0.4mg intramuscular) on an opioid agonist dose in non-dependent opioid users, with variation of the opioid agonist across sessions. The second design could test the subjective onset of action of naloxone using a naloxone dose-escalation series across multiple sessions in dependent opioid users. Analogous to signal detection studies, the naloxone dose-escalation series could be interspersed with random placebo sessions to capture accuracy of the self-report data. Experimental study of low-dose naloxone in an opioid-using population would provide the distinct advantage that the onset of brain effect could be detected very sensitively, alongside blood plasma concentrations.

At least two studies have previously been conducted in opioid-dependent volunteers to assess the pharmacodynamics of intranasal naloxone (Loimer et al., 1992; Loimer et al., 1994). However, this research almost certainly violated ethical standards for studies in vulnerable populations: intravenous (1mg) and intranasal (1mg/0.4mL) naloxone was administered to prisoners in Pakistan as opioid challenge test, i.e. with the aim to induce opioid withdrawal symptoms.

I have been awarded a Society for the Study of Addiction Travelling Scholarship to undertake a research visit with Professor Sandra Comer at the Substance Use Research Center at Columbia University (New York, USA) in July 2017. A primary focus of Professor Comer's lab is the study of opioid agonists and antagonists using a preclinical human laboratory model. The basic tenet of this model is that – in order to determine the potential utility of a medication for opioid dependence – the effects of the medication on opioid use must be studied directly in the user population. This line of research is intrinsically challenging.

During the research visit, I will develop a discussion paper (in collaboration with Professor Comer, my PhD supervisor Professor Sir John Strang, and Drs. Joanne Neale and Charlotte Tompkins) which will explore the challenges of conducting experimental medicine trials, including naloxone studies, in opioid user populations. This discussion paper will draw on experiences at Professor Comer's lab as well as on a qualitative study for which we have recently concluded the interviews ("Patient perceptions and experiences of different types of medication formulation"; REC reference: 17/SC/0037) involving focus groups with opioid users that Dr. Charlotte Tompkins and I jointly conducted in South London between March and May 2017. A central part of the focus groups was dedicated to the discussion of what, if any, study designs and conditions

could be feasible and ethically sound for potentially testing the pharmacodynamics of naloxone to inform dosing in clinical practice.

10.5.3 Take-home naloxone: Models for implementation

Implementation research will be necessary as take-home naloxone programs progressively move into new settings. One such feasibility study is currently being undertaken in correctional and reentry settings in California, where stakeholder interviews and focus groups are being conducted to address take-home naloxone implementation barriers (NIH project number: 5R34DA039101-02).

Research is also needed to compare systematically different settings and distribution models for take-home naloxone to identify those with biggest reach among target populations. Take-home naloxone implementation studies have mostly recruited heroin users via urban harm reduction infrastructures, including needle exchange schemes. Implementation studies are needed for emerging target groups such as rural user populations and prescription opioid users (including chronic pain patients) whose overdose risk awareness may be low (Albert et al., 2011; Coffin et al., 2016; Compton & Volkow, 2006; Paulozzi & Ryan, 2006). Community pharmacy-based naloxone has been piloted as a means by which to promote naloxone access in rural areas (T.C. Green, Dauria, Bratberg, Davis, & Walley, 2015). It will be important to examine the demographics of prescription opioid users (including chronic pain patients) in greater detail (Coffin et al., 2016; Ling, 2017; Volkow & McLellan, 2016) to identify high-yield implementation strategies.

10.5.4 Take-home naloxone: Opioid user engagement

Despite increasing take-home naloxone provision among (recent) injecting drug users from 8% (2006-10 baseline) to 51% (2014-2015) (Bird et al., 2017), the Scottish National Naloxone Programme reported naloxone carriage rates of only 5-16% (A. McAuley et al., 2016), highlighting the need to improve user engagement in take-home naloxone programs and to ensure their understanding of, and adherence to, the importance of having emergency naloxone always at hand..

Qualitative research may help shed light onto barriers to take-home naloxone intervention uptake. While opioid users in Baltimore and Chicago reported predominantly positive interactions with police and paramedics (Sherman et al., 2008) and expressed interest in take-home naloxone provision as well as willingness to share information on overdose emergency management with peers and family members (Sherman et al., 2009), naloxone experiences likely differ. Qualitative interviews conducted in Scottish cities in 1997-99 (Neale & Strang, 2015) revealed opiate users' negative views of naloxone and accounts of harm caused by its administration (e.g. acute withdrawal, aggression, self-discharge and further drug-seeking), even though this was not apparent in observational data. Similarly, opioid users in New York and Los Angeles reported fear of withdrawal and police involvement as key concerns associated with take-home naloxone distribution (Lankenau et al., 2013; Worthington et al., 2006), and continued use of folk remedies posed a barrier to take-home naloxone use (Lankenau et al., 2013). Reasons for poor naloxone implementation need to be understood (Black et al., 2017), and systematic study of lived naloxone experiences is needed to identify strategies to increase user engagement in take-home naloxone programs.

10.5.5 Take-home naloxone: Carriage rates

As mentioned in the previous section, naloxone carriage rates of only 5-16% were reported for the Scottish National Naloxone Programme among a sample of injecting drug users (McAuley et al., 2016). Low naloxone carriage rates pose a major concern as they suggest low probability of naloxone availability at the time of an overdose. There are at least three possible explanations for the observed low carriage rates in the McAuley et al. study (2016) that warrant further study.

Firstly, carriage rates were lowest among those not recently injecting. Is it possible that naloxone carriage is associated with current injecting behavior and perceived personal risk of experiencing an overdose? Such potential optimism bias in opioid users (Sharot, Guitart-Masip, Korn, Chowdhury, & Dolan, 2012) would be very risky considering that risk of overdose is pronounced following periods of abstinence (see Chapter 2).

Secondly, the data showed a negative association between volume of community-wide take-home naloxone distribution (observed increase) and individual naloxone carriage (observed decrease). Do take-home naloxone recipients find it is less important to carry

their individual naloxone kit when the perceived overall availability of naloxone kits in their community has gone up? If so, the risks of such diffusion of responsibility need to be addressed as part of the curriculum of overdose prevention training.

Finally, the authors cite the physical properties (e.g. size, weight) of the Prenoxad injectable naloxone kits distributed in Scotland as possible reason for low carriage (McAuley et al., 2016). While it is generally assumed that the introduction of non-injectable naloxone products would lead to higher carriage and usage rates, this has yet to be empirically studied.

Starting in June 2017, I will conduct an electronic survey of potential opioid overdose witnesses in the UK and at least four European countries (n=500) with the aim to assess naloxone device preference and likelihood of carriage and use among relevant sub-populations (opioid users, family members, peers, service staff). Naloxone devices presented as stimulus material in the survey will comprise ampoules, pre-filled syringes, improvised nasal kits, purpose-developed nasal spray (Aptar device, see Chapter 4), and the buccal tablet (see Chapter 9). It is anticipated that the results of this survey-based exploratory study of the naloxone device-user interaction will inform policymakers, clinicians, as well as those developing new naloxone medications, regarding which naloxone devices will have suitability and acceptability among the sub-populations of potential overdose witnesses in different countries.

10.6 Conclusion

Despite demonstrable benefits, take-home naloxone remains underused as a public health strategy. To date, its distribution has mostly been made possible by community-based harm reduction organizations with limited central funding. To tackle the rising numbers of opioid-related deaths internationally, governments and non-governmental organizations will need to provide political leadership and perhaps specific financial support to improve the necessary extent of coverage of this potentially life-saving intervention.

Take-home naloxone needs to be embedded into an evidence-based harm reduction strategy that promotes access to opioid substitution treatment and clean needles to reduce the spread of infectious diseases and the incidence of overdose deaths. As a

low-threshold intervention, take-home naloxone becomes particularly important where opioid substitution treatment is not available or not accessed. Accordingly, its impact on opioid overdose mortality is likely greatest among those not enrolled in treatment.

At the time of submission of this thesis, the prevalence rates of opioid overdose mortality in the UK and the US (see Preface) show no signs of slowing down. Politically, both countries are at a crossroads.

The impact of the upcoming UK general election on June 8, 2017 and of Brexit negotiations on public health is unknown. It remains to be seen whether a weakening currency and changes to existing trade agreements will impact the cost of imported drugs and medical equipment, and whether restrictive immigration policies will lead to NHS staff shortages (Gulland, 2017; Majeed, 2017; Modi, 2017; Simpkin & Mossialos, 2017). If so, such challenges may add to the pressures of ongoing austerity policy that have already affected the commissioning of drug treatment services and the lives of patients (PHE, 2014).

In the US, the House of Representatives voted to repeal the [Patient Protection and] Affordable Care Act (ACA) on May 4, 2017. The ACA had been signed into law by President Obama in March 2010 and included two central provisions that facilitated access to opioid substitution treatment (Friedmann, Andrews, & Humphreys, 2017). Health insurance coverage was significantly increased through Medicaid expansion as well as private insurance, and insurance plans were required to cover treatment for opioid use disorder at parity with treatment for medical or surgical procedures. It is estimated that by 2016 the ACA had expanded health insurance to close to 700,000 patients with opioid use disorder (Friedmann et al., 2017). On May 9, 2017, US Secretary of Health and Human Services Dr. Tom Price reportedly lauded faith-based programs during his visit to West Virginia (Eyre, 2017), i.e. the state with the highest per capita rate of opioid overdose mortality (CDC, 2016a), announcing: "If we're just substituting one opioid for another, we're not moving the dial much. […] Folks need to be cured." On May 23, 2017, the Trump administration released its 2018 budget request. The budget plan seeks to cut funding for the US Centers for Disease Control and Prevention by 17 percent (Achenbach & Sun, 2017) and additionally proposes to cut Medicaid funding by US $800 billion over the next decade (Paletta, 2017). According to the Congressional Budget Office, an estimated 23 million US residents would lose health insurance by 2028 (Lowes, 2017).

It is uncertain how the UK and US drug treatment landscapes may change in the coming years. However, in consideration of the above scenarios, it appears unlikely that the need for take-home naloxone will diminish.

Naloxone was, until recently, only licensed as injection, but its reformulation and the arrival of non-injectable naloxone may bring about change and possibly greatly improved impact. Concentrated nasal spray offers multiple implementation advantages and has the potential to significantly increase community-based naloxone availability, carriage rates, and use.

I hope that the evidence presented in this thesis will reduce barriers to naloxone access among those in need and, ultimately, contribute to reducing the number of preventable opioid overdose deaths – such as the case of Dr. Fishman's son and so many others.

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Appendix A. Ethical Approval Letters

South Central - Berkshire B Research Ethics Committee
Whitefriars
Level 3, Block B
Lewins Mead
Bristol
BS1 2NT

Telephone: 0117 342 1382

01 March 2016
Reissued 02 March 2016 – including insurance document & GP letter

Dr Ulrike Lorch
Richmond Pharmacology Ltd.
Cranmer Terrace, Tooting
London
SW17 0RE

Dear Dr Lorch

Study title:	**A 5-part, open-label, randomised, single dose, crossover study in healthy subjects to compare the pharmacokinetics of a single dose of intranasal MR903 (1 mg, 2 mg and 4 mg) and naloxone hydrochloride given as a 0.4 mg intramuscular and 0.4 mg intravenous dose**
REC reference:	**16/SC/0033**
Protocol number:	**MR903-1501**
EudraCT number:	**2015-004493-15**
IRAS project ID:	**197836**

Thank you for your letter of 23rd February 2016, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the REC Manager, Tina Cavaliere, nrescommittee.southcentral-berkshireb@nhs.net

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

You should notify the REC once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. Revised documents should be submitted to the REC electronically from IRAS. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which you can make available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

Clinical trial authorisation must be obtained from the Medicines and Healthcare products Regulatory Agency (MHRA).

The sponsor is asked to provide the Committee with a copy of the notice from the MHRA, either confirming clinical trial authorisation or giving grounds for non-acceptance, as soon as this is available.

The sponsor must ensure that all participants enrolled into the study are registered with The Over Volunteering Prevention System (TOPS).

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites listed in the application, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

I am pleased to confirm that the favourable opinion applies to the following research site(s), subject to site management permission being obtained prior to the start of the study at the site (see under 'Conditions of the favourable opinion below').

Research site	*Principal Investigator / Local Collaborator*
Richmond Pharmacology Ltd	Dr Ulrike Lorch

Plans to include any new sites in the study in addition to those listed in the application should be notified to the Committee as a substantial amendment. The study should not start at the new site until ethical approval and site management permission is obtained.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Copies of advertisement materials for research participants [email/website advert]	2.0	20 January 2016
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [MR903-1501_Indemnity]		07 January 2016
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [MR903-1501_C15047 Statement of Insurance Cover]		08 January 2016
Investigator's brochure / IMP Dossier [MR903 IB]	1.0	18 January 2016
GP/consultant information sheets or letters [RPL GP Fax Cover Letter template]	3.0	17 October 2013
IRAS Checklist XML [Checklist_23022016]		23 February 2016
Other [MR903-1501 Genetic Consent form]	1.0	29 January 2016
Other [RPL Unit Rules]	2.0	12 May 2006
Other [RPL Vol Charter]	5.0	10 June 2015
Other [RPL Certificate Insurance]		28 April 2015
Other [RPL Ph 1 accred cert]		13 March 2015
Other [MR903-1501 Certificate of Insurance Cover]		30 December 2015
Other [MR903-1501 EC Phase 1 letter]		25 January 2016

Other [Evidence of GMC registration for PI]		29 January 2016
Other [Scientific Advice Naloxone(MR903)]		19 November 2015
Other [MR903-1501 Protocol Signature Page MRL]		08 January 2016
Other [RE_ Phase 1 generic review _ 285]		21 October 2015
Other [NEW_MR903-1501_C15047 Protocol_tracked changes]	2.0	22 February 2016
Other [NEW_MR903-1501_C15047 Protocol including Protocol Amendment No 1_fully signed]	2.0	22 February 2016
Other [NEW_MR903-1501_C15047_Participant Information and Informed Consent_tracked]	2.0	19 February 2016
Other [NEW_MR903-1501_C15047_Participant Information and Informed Consent]	2.0	19 February 2016
Other [NEW_RPL GP Consent Form]	4.0	16 October 2015
Other [NEW_RPL_Standard GP Fax Cover for Medical Summary]	1.0	07 November 2014
Other [NEW_MR903-1501_C15047_Response to provisional opinion letter]		23 February 2016
REC Application Form [REC_Form_29012016]		29 January 2016
Summary CV for Chief Investigator (CI) [Dr Ulrike Lorch]		01 May 2015
Summary of product characteristics (SmPC) [Baun Naloxone]		16 July 2014

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

16/SC/0033	Please quote this number on all correspondence

With the Committee's best wishes for the success of this project.

Yours sincerely

Pp 

Dr John Sheridan
Chair

Email: nrescommittee.southcentral-berkshireb@nhs.net

Enclosures: "After ethical review – guidance for researchers"

Copy to: *Dr Emma Akuffo*

NHS
Health Research Authority
NRES Committee London - London Bridge
Skipton House
80 London Road
London
SE1 6LH

Telephone: 020 7972 2582

23 March 2015

Prof John Strang
Addictions Science Building
4 Windsor Walk
London
SE5 8AF

Dear Prof Strang

Study title:	**A Pilot, Phase 1, Open-Labelled, 4 Period, Randomised, Crossover Study to Evaluate the Pharmacokinetics of Naloxone when Given by the IV, IM and Buccal Routes of Administration in Healthy Male Subjects**
REC reference:	**15/LO/0103**
Protocol number:	**KCL/NALOX/01/14**
EudraCT number:	**2014-001802-16**
IRAS project ID:	**125173**

Thank you for your letter of 09 March 2015, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Manager, Stephanie Hill, nrescommittee.london-londonbridge@nhs.net. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from NRES. Guidance on where to register is provided on the HRA website.

Clinical trial authorisation must be obtained from the Medicines and Healthcare products Regulatory Agency (MHRA).

The sponsor is asked to provide the Committee with a copy of the notice from the MHRA, either confirming clinical trial authorisation or giving grounds for non-acceptance, as soon as this is available.

The sponsor must ensure that all participants enrolled into the study are registered with The Over Volunteering Prevention System (TOPS).

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites listed in the application, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering letter on headed paper [Cover letter]	1	23 December 2014
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Insurance letter]	1	14 July 2014
GP/consultant information sheets or letters [GP letter]	1	22 December 2014
Letters of invitation to participant [Letters of invitation to participant]	1	22 December 2014
Other [CV David Taylor]	1	08 December 2014
Other [CV Rebecca McDonald]	1	23 December 2014
Participant consent form [Participant consent form]	4	07 March 2015
Participant information sheet (PIS) [Participant information sheet]	4	07 March 2015
REC Application Form [REC_Form_05012015]		05 January 2015
Referee's report or other scientific critique report [MHRA authorisation letter]	Final	26 November 2014
Research protocol or project proposal [Research Protocol]	2.1	30 September 2014
Sample diary card/patient card [Sample patient card]	1	23 December 2014
Summary CV for Chief Investigator (CI) [Summary CV for CI (John Strang)]	Final	05 December 2014
Summary of product characteristics (SmPC) [SmPC Naloxone-Hydrochloride]	Final	11 November 2005

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

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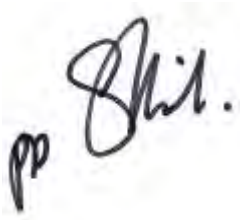
15/LO/0103	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely



Dr Michael Goggin
Alternate Vice-Chair

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Enclosures: "After ethical review – guidance for researchers" *[SL-AR1]*

Copy to: *Ms Jenny Liebscher, King's College London, Institute of Psychiatry*

Appendix B. First-Authored Publications

Drug and Alcohol Dependence xxx (2017) xxx-xxx

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Review

Twenty years of take-home naloxone for the prevention of overdose deaths from heroin and other opioids Conception and maturation

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ARTICLE INFO

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ABSTRACT

Background: Opioid overdose is a major cause of mortality, but injury and fatal outcomes can be prevented by timely administration of the opioid antagonist naloxone. Pre-provision of naloxone to opioid users and family members (take-home naloxone, THN) was first proposed in 1996, and WHO Guidelines were issued in 2014. While widespread in some countries, THN is minimally available or absent elsewhere. This review traces the development of THN over twenty years, from speculative harm reduction proposal to public health strategy.
Method: Medline and PsycINFO were searched for peer-reviewed literature (1990 2016) using Boolean queries: 1) naloxone OR Narcan ; 2) (opioid OR opiate) AND overdose AND prevention . Grey literature and specialist websites were also searched. Data were extracted and synthesized as narrative review, with key events presented as chronological timeline.
Results: Results are presented in 5-year intervals, starting with the original proposal and THN pilots from 1996 to 2001. Lack of familiarity with THN challenged early distribution schemes (2001 2006), leading to further testing, evaluation, and assessment of challenges and perceived medicolegal barriers. From 2006 2011, response to social and legal concerns led to the expansion of THN programs; followed by high-impact research and efforts to widen THN availability from 2011 to 2016.
Conclusions: Framed as a public health tool for harm reduction, THN has overcome social, clinical, and legal barriers in many jurisdictions. Nonetheless, the rising death toll of opioid overdose illustrates that current THN coverage is insufficient, and greater public investment in overdose prevention will be required if THN is to achieve its full potential impact.

1. Introduction

Over the past two decades, take-home naloxone (THN) has moved from its initial conceptualization as harm reduction measure for preventing opioid overdose deaths to becoming an evidence-based public health strategy with organized implementation (UNODC/WHO, 2013). Strong advocacy by local early adopters has enabled emergence of THN initiatives around the world. In Italy, a harm reduction service on the outskirts of Turin reportedly provided naloxone access to clients as early as 1991 (ForumDroghe, 2016). Today, formal THN programs exist in Australia, Canada, at least nine European countries (EMCDDA, 2016), and the US; as well as pilots in low- and middle-income countries, including Afghanistan, China, India, Kazakhstan, Kyrgyzstan, Russia, Tajikistan, Thailand, Ukraine, and Vietnam (UNODC/WHO, 2013). The World Health Organization issued new guidelines for community-based overdose management, suggesting that [p]eople likely to witness an opioid overdose should have access to naloxone and be instructed in its administration (WHO, 2014).

Despite these recent advances, dissemination of THN remains remarkably slow. THN was first proposed in 1996, and it was not until the late 2000 s that serious consideration of THN implementation at state or national level began.

Opioid overdose continues to account for approximately 68,000 104,000 annual deaths worldwide (UNODC, 2016b), with

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0376-8716/

sharp increases reported for the UK (ISD, 2016; ONS, 2016) and US (CDC, 2016). Many of these deaths could be prevented if THN was available: A recent analysis of the time course of opiate metabolites post-mortem found that survival times post-injecting exceeded 20 30 min in the majority of heroin overdose deaths (Darke and Duflou, 2016), suggesting that there is indeed sufficient time to intervene (Darke and Duflou, 2016; Tas and McDonald, 2016). However, adequate intervention is only possible where witnesses recognize the opioid overdose. In addition to naloxone supply, it is thus essential for THN programs to teach awareness of overdose risk factors (e.g., using alone, street injection), crisis detection (e.g., snoring following opioid use may signal overdose), interim emergency care aid, and need for continued care (McAuley et al., 2010; Seal et al., 2005; Strang et al., 2008a).

This brief history chronicles major milestones and events in the emergence and evolution of THN.

2. Method

2.1. Literature search

The first author (RM) searched Medline and PsycINFO for THN-related peer-reviewed literature published between January 1990 and December 2016 using the Boolean queries: 1) naloxone OR Narcan ; 2) (opioid OR opiate) AND overdose AND prevention . Specialist websites and databases of Public Health England, the European Monitoring Centre for Drugs and Drug Addiction, US National Institute on Drug Abuse, and United Nations agencies were also searched for THN-related entries. Additional materials from the non-peer-reviewed literature were consulted to reconstruct the historical timeline.

2.2. Data extraction and evidence synthesis

THN-related evidence was extracted and synthesized as narrative review by all three authors (RM, NC, JS). Relevant events were considered according to occurrence in one of four developmental phases of constructed quinquennia (with some overlap naturally occurring), which cover the 20-year period from 1996 to 2016.

3. Results

We present results in four sections which discuss the following themes. Firstly, we examine formal articulation of the need for THN, along with preliminary testing and implementation (1996 2001; Section 3.1). We then document early THN schemes and challenges (2001 06; Section 3.2). We then explore new national or state-level naloxone programs made possible through the identification and response to legal concerns (2006 11; Section 3.3). Finally, we review the emergence of research studies meeting higher evidentiary standards and examine efforts to widen THN availability (2011 16; Section 3.4). Key events are also summarized as a chronological timeline (see Table 1).

3.1. 1996-2001 circa: conception, testing the notion, and early implementation

3.1.1. Original articulation

Naloxone was first synthesized and patented in the early 1960s (Blumberg et al., 1961; Lewenstein and Fishman, 1966) and FDA-approved in 1971 for intravenous, intramuscular, and subcutaneous administration for partial or complete reversal of opioid overdose (Garfield, 1983) (see Table 1). Although not the first opiate antago-

Table 1
Key events in the emergence and evolution of take-home naloxone.

Year	Month	Country	Event
1961	March	USA	Drs. Jack Fishman and Mozes J. Lewenstein apply for first US patent for synthesis of naloxone (issued in May 1966)
		USA	Dr. Harold Blumberg and colleagues publish abstract in *Federation Proceedings* in which he introduces naloxone as potent, rapid-acting, and relatively pure narcotic antagonist.
1962	March	UK	Sankyo applies for British patent for naloxone (issued in October 1963)
		Japan	Minakami et al. of Sankyo Company Ltd. Publish first full-length journal article on naloxone in *Life Sciences*
1971		USA	FDA licenses naloxone as prescription-only medication; naloxone enters clinical practice in Europe in subsequent years
1983		Int l	Naloxone is included in the 1983 WHO List of Essential Medicines (and subsequent editions)
1991		Italy	Report of community-based naloxone access in Turin suburb
1992	March	Australia	Notion of THN provision to at-risk populations is mooted at 3rd International Harm Reduction Conference in Melbourne
1996	June	UK	*BMJ* editorial by Strang et al. states home-based supplies of naloxone would save lives
	ca. June	USA	Chicago Recovery Alliance (CRA) distributes first THN kits
		Italy	Ministry of Health classifies naloxone as over-the-counter medication
		Italy	Reports of THN distribution in Padua
1998	September	Italy	Simini announces plans to distribute THN in Bologna and surrounding Emilia Romagna region in *The Lancet*
	October	UK	Island of Jersey starts THN distribution
1999	January	Germany	Fixpunkt Berlin starts THN distribution
	March	USA	San Francisco Needle Exchange starts THN distribution
2001	April	Germany/UK	First published report of THN distribution by Dettmer et al. in *BMJ*
		Spain	Reports of underground THN distribution in Barcelona
		USA	New Mexico launches THN program
		UK	Introduction of first mainland THN scheme (south London)
2002	March	USA	Dan Bigg of CRA reports first lives saved using THN in *BMJ*

Table 1 (*Continued*)

Year	Month	Country	Event
2003		USA	San Francisco Public Health Dept. starts THN program
2004	June	USA	Lower East Side Harm Reduction Coalition in New York starts THN distribution
		USA	Baltimore launches Staying Alive Drug Overdose Prevention Program
2005	November	UK	Legal status of naloxone changed to permit emergency administration of naloxone by any member of the general public (Schedule 7 of the Medicines Act)
2006	August	USA	Boston Public Health Commission authorizes start of THN program, including provision of intranasal naloxone kits
2006		UK	National Treatment Agency for Substance Misuse (NTA) funds THN training pilot in 16 sites in England
2007		UK	Scotland and Wales establish THN pilots
2008		UK	Medical Research Council funds N-ALIVE trial
		Spain	Formal THN program launched in Barcelona
2010		USA	ONDCP National Drug Control Strategy endorses community use of naloxone
	November	UK	Scotland launches national THN program
2011		UK	Scottish Lord Advocate issues new guidelines
		UK	Wales launches national THN program
		Australia	First Australian THN program starts in Canberra
2012	March	Int l	UNODC Resolution 55/7 states opioid overdose treatment, including the provision of opioid receptor antagonists such as naloxone, is part of a comprehensive approach to services for drug users
	April	USA	FDA, CDC, NIDA, and HHS convene naloxone meeting
	May	UK	Advisory Council on the Misuse of Drugs urges Department of Health to review naloxone prescription-only status
	December	Australia	Naloxone is added to the Pharmaceutical Benefit Scheme
2013	March	Denmark	THN program starts (dual kits: intranasal and injectable)
		Estonia	Harju and East-Viru counties start THN distribution
2014	July	Norway	THN program starts (intranasal)
	November	Int l	WHO releases guidelines on the community management of opioid overdose
2015	May	Ireland	Health Services Executive approves THN by prescription, THN project starts
	October	UK	Public Health England release guidelines allowing drug services to issue THN without prescription
	November	USA	FDA approves a first naloxone nasal spray product
2016	February	Australia	Injectable naloxone becomes available over-the-counter
	April	Int l	UNGASS 2016 includes naloxone in its scientific summary
	October	Canada	Health Canada approves naloxone nasal spray product without prescription requirement
	October	USA	FDA convenes meeting to discuss naloxone dosing standards

nist, naloxone was the first largely free of agonist effects. Naloxone became standard rescue medication in emergency management of heroin overdose in hospital and ambulance settings and has been included in the WHO List of Essential Medicines since 1983 (WHO, 2011, 2014).

The idea to enable opioid users and/or family and friends to take naloxone home did not arise until more than two decades after initial FDA-approval. It was first mooted at the 3rd International Harm Reduction Conference in March 1992 (Strang, 1992, 1993; Strang and Farrell, 1992) as a mere throwaway example of harm reduction alternatives that were being overlooked. However, the first serious consideration of THN was in the 1996 BMJ editorial (Strang et al., 1996) which identified key elements of the intervention, including provision to: (1) individuals at high risk of overdose, e.g., those leaving emergency care following overdose and those who lost tolerance due to detoxification, incarceration, or abstinence-based treatment; (2) patients enrolled in treatment programs (despite treatments protective benefits, they remain at risk); and (3) active users.

The editorial also described the poor suitability of existing naloxone products (ampoules, vials) compared to pre-filled syringes and identified medico-legal challenges raised by the prospect of third parties, such as family members, requesting or administering naloxone. Finally, the editorial urged reconsideration of naloxone s prescription-only medication status. These central points of the editorial shaped implementation and research in the subsequent years.

3.1.2. Early implementation

The introduction of THN was made possible through user advocates working with physicians willing to prescribe naloxone despite medicolegal barriers. First THN provision occurred in the late 1990s, in the United States (Chicago, San Francisco), Germany (Berlin), the UK (Jersey), and Italy (Turin, Bologna, Padua).

3.1.2.1. United States The Chicago Recovery Alliance (CRA) began obtaining and distributing naloxone in 1996. Due to high user demand during a fourfold increase in drug-related deaths from 1996 to 2000, distribution by mobile van was introduced in 1998 and converted into a formal training curriculum in 2001 (Bigg, 2002).

During the late 1990s, CRA began discussions with harm reduction advocates in other places around starting THN-programs and served as central clearinghouse for THN across the US.

San Francisco Needle Exchange introduced a small-scale THN pilot for youth in the Haight-Ashbury district in 1999 (Bigg, 2000; Giuliano, 2000; Seal et al., 2001). The pilot was later scaled up in conjunction with the DOPE (Drug Overdose Prevention and Education) project (Giuliano, 2000; Seal et al., 2001) and moved to the San Francisco Public Health Department in 2003.

In 2000, the Drug Policy Alliance (formerly Lindesmith Center) partnered with the University of Washington Alcohol and Drug Abuse Institute to explore pragmatic approaches to Preventing Heroin Overdose, which included sessions on naloxone distribution.

3.1.2.2. Continental Europe Multiple sources point to largely undocumented early community-based naloxone availability in parts of Italy, notably Turin (1991) and the Emilia Romagna region (incl. Bologna, 1998) (ForumDroghe, 2016; Simini, 1998).

There were reports of THN distribution in Padua in 1996, where a methadone clinic distributed 150 naloxone vials within 18 months. While overdose deaths decreased citywide, there was no formal evaluation of THN usage (Schifano, 2001).

Two pilot schemes in Berlin and the British island of Jersey (Dettmer et al., 2001) constitute the first published outcomes report on THN provision. Between 1998 and 2000, 101 clients of a community-based drug clinic in Jersey were trained in overdose management and received THN kits, with five reported overdose reversals (Dettmer et al., 2001). In Berlin, THN was introduced at a mobile needle and syringe exchange scheme (Fixpunkt) in 1999. Within 16 months, 124 THN kits had been issued; 22 users reported administering naloxone for a total of 29 overdose reversals (Dettmer et al., 2001). The article attracted support but also sharp criticism (Ashworth, 2001; Blackwood, 2001; Mountain, 2001), noting low response rate and the lack of systematic follow-up, objective mortality data, and risk assessment concerns echoed in the THN debate throughout the 2000s. The Berlin pilot was discontinued after 2002 due to lack of funding (AIDS-Hilfe, 2013; Dettmer, 2014).

3.1.3. Testing the notion: is the intervention necessary?

Several studies in the late 1990s and early 2000s identified situations in which naloxone should be made available:

3.1.3.1. Injecting use In a London-based community sample of heroin users, the vast majority of reported overdoses occurred among injection users (Gossop et al., 1996). Injecting bears a much higher risk of fatal overdose than chasing the dragon (i.e., inhalation following sublimation with heat) (Strang et al., 1997), snorting or oral use. (It was later estimated that one in four injecting drug users would experience an overdose each year (Darke et al., 2003)).

3.1.3.2. Return into the community An influential early study by Seaman et al. (1998) identified the period following release from prison as the most striking high-risk situation, with within two weeks of release (Bird and Hutchinson, 2003). (The finding of increased risk up to four weeks post prison release was subsequently quantified as 1 in 200 prisoners with history of heroin use dying from opioid overdose in the first two weeks post-release and was replicated internationally (Merrall et al., 2010). Similar but less intense concentrations of overdose deaths were subsequently also observed among patients completing in-patient detoxification (Strang et al., 2003), residential rehabilitation (Davoli et al., 2007), and hospital/residential treatment (Merrall et al., 2013; Ravndal and Amundsen, 2010)).

3.1.3.3. Opioid agonist treatment The first weeks on oral methadone treatment were found to be associated with a transient increase in risk of overdose death (Caplehorn, 1998; Caplehorn and Drummer, 1999).

3.1.4. Testing the notion: is the intervention acceptable for those involved?

Parallel to early THN implementation, research assessed the feasibility and acceptability among users, carers and providers.

3.1.4.1. Opioid users The 1996 BMJ editorial identified opiate users as the primary target group for THN because they are at risk of future overdose themselves and highly likely to witness and intervene in someone else s overdose. Users have expressed strong support of THN. A London-based survey of injecting drug users (Strang et al., 1999) estimated that two-thirds of witnessed overdose deaths could have been avoided with THN. Most respondents had already witnessed at least one overdose; 89% expressed willingness to administer naloxone in the event of an overdose; 70% agreed with the proposal that naloxone should be provided; and nearly 90% of those who had witnessed an overdose stated that they would have used the medication had it been available. Subsequent interview studies identified opioid users willingness to be trained in overdose management and naloxone administration (Bennett and Higgins, 1999; Strang et al., 2000).

3.1.4.2. Carers Most opiate overdoses occur at private homes and/or in presence of peers, family members, and partners (Best et al., 2002; McGregor et al., 1998). Constituting a potential intervention resource, close contacts of users are thus the second target group for THN and training.

3.1.4.3. Health care providers An early US legal analysis (Burris et al., 2001) found that providers risk of malpractice liability associated with prescribing THN was no greater than for general health care provision. Prescribing THN to an at-risk patient for administration by a trained partner/family member is analogous to the pre-provision of anti-epileptic medication or injectable adrenaline/epinephrine (EpiPen). However, in situations where naloxone is being prescribed without specific knowledge of who will administer or be administered naloxone, the legal situation becomes murky.

US providers voiced strong concerns over uncertain medico-legal status and potential liability issues and expressed anxieties about patients deputation as health care providers when injecting naloxone (Burris et al., 2001). Around the same time, Australian providers and service users alike raised concerns about civil or criminal liability (Lenton and Hargreaves, 2000).

3.1.5. Thinking at the national level

In 2000, THN provision received an early public endorsement by the UK Advisory Council on the Misuse of Drugs (ACMD, 2000) who stated: Our view is that, as a matter of principle, naloxone should be made more widely available (that is beyond hospital, paramedic and ambulance settings) [ ] . The statutory advisory body gave clear direction on the need for: (1) enhanced attention to effective overdose management by emergency medical services, including authorization of lower grades of ambulance staff to administer naloxone; (2) uniform agreement that an overdose is primarily a medical emergency (which ordinarily should not involve police attendance); (3) treatment agencies to be teaching overdose management, (4) naloxone to be widely given to friends and partners of drug users, (5) naloxone provision to be extended to prisons and police stations for use by trained staff.

The vision articulated in the ACMD report would shape the naloxone policy debate up to the present (see Table 2).

3.2. 2001–2006 circa: modest progress amidst concerns over the safety and legality of the intervention

Following the pioneering CRA program, early adopters in the United States included New Mexico, which began THN distribution in early 2001 (Baca and Grant, 2005).

In 2004, the Baltimore Staying Alive Drug Overdose Prevention Program was launched, sponsored by the Baltimore City Health Department and Open Society Institute, and the Lower East Side Harm

Table 2
| Key statements from the 2000 UK ACMD report, as they relate to target audiences involved in the prevention of opioid overdose deaths.

Target audience	Statement
Opioid users and peers	We believe that heroin and other opioid users, who are most likely to be witnesses to their friends' overdoses, should be given guidance on what to do in those circumstances. (p. 80)
	[N]aloxone should be made more generally available, for example, to those who are likely to witness opioid overdoses. This would involve a supply of the drug being kept at home, and advice being given to friends and partners of the drug users on its emergency use. (p. 80)
	If it was accepted that this wider availability of naloxone was desirable there would be a need to ensure, through training, that the drug was administered correctly and in the right circumstances; that it was seen only as part of a larger resuscitative response; that fresh supplies were regularly introduced; and that proper arrangements were in place for its prescription, including to whom it might be administered. (p. 81)
Primary care	Specific interventions available to primary care include [ ] response to overdoses (p. 78)
Emergency Departments	[H]ospitals should satisfy themselves that the arrangements [for staff training or treatment protocols] [for treating opioid overdoses] [in A & E departments] are satisfactory. (p. 79)
	[T]he fact that [A&E departments] see overdosers who have not died and who are subsequently discharged, is an opportunity which we think must be exploited more vigorously. Many such attenders are repeat attenders. (p. 78)
Ambulance/Police	Our view is that a call to a person who has overdosed should be regarded by the ambulance and police services as a *medical emergency* in the first instance, rather than as a call to the scene of a crime. It follows that we do not believe that ambulance services should, as a matter of course, inform the police when they are called to a drug overdose. (p. 79)
	We think it is probably unrealistic to expect police forces to give a blanket guarantee that witnesses to an overdose will not be prosecuted if officers attend. On the other hand, we think that should be the general presumption. (p. 79)
Police/Prisons	[N]aloxone might also be made available to prison healthcare staff. And it should be kept at police stations which have custody suites for emergency use by medical staff and other trained personnel. (p. 80)

Reduction Coalition in New York conducted a pilot, which was expanded to all city-funded Syringe Exchange Programs in 2005 (Heller and Stancliff, 2007).

In Europe, there were reports of THN distribution in Barcelona as early as 2001 (Trujols, 2001). In mainland UK, THN was first introduced in South London in mid-2001 (Strang, 2001).

3.2.1. Training opioid users and their family members

In the first published evaluation of THN training, Seal et al. (2005) assessed knowledge of overdose management by asking participants to name risk factors, signs of overdose, and overdose prevention and management strategies. A significant increase in knowledge was maintained at 6-month follow-up (Seal et al., 2005). Despite willingness to participate in THN training, opioid users also expressed concerns about THN, such as fear of experiencing withdrawal symptoms, enabling further drug use, risk of blood-borne virus infection, and potentially having to manage agitation and hostility in those revived (Kerr et al., 2008; Seal et al., 2003; Worthington et al., 2006). Service users also expressed concerns about the risk of confiscation of the antidote and its potential role in escalating already delicate relationships with law enforcement (Seal et al., 2003; Worthington et al., 2006).

In an England-based postal survey (Strang et al., 2008b), the majority of family members expressed strong interest in THN training.

3.2.2. Providers' concerns

Support was weak in the drug treatment field, where the debate was dominated by legal and safety concerns. Providers questioned users competency in naloxone administration and pointed to the risk of unsafe needle disposal (Ashworth, 2006; Byrne, 2006; Tobin et al., 2005). Even though an early survey of drug users had found that THN was unlikely to lead to increased heroin consumption (Strang, 1999), a common concern among providers was potential promotion of drug use (Ashworth, 2006; Tobin et al., 2005). Negative attitudes were revealed in surveys of Baltimore-based emergency service providers (Tobin et al., 2005) and physicians throughout the US who were likely involved in treatment of opioid users (Beletsky et al., 2007): most believed THN would not reduce drug-related deaths and reported they would never consider prescribing naloxone. A notable exception was a postal survey of New York-based clinicians of whom over a third were willing to prescribe naloxone (Coffin Fuller et al., 2003).

3.3. 2006–2011 circa: identification of legal pathways for take-home naloxone and first national and state-wide programs

3.3.1. Responses to legal barriers

Because THN has come about so recently, most medico-legal barriers to it were unintended consequences of prior legislation passed for other purposes (NPHL, 2016). About ten years after the original THN proposal, some jurisdictions began to pass laws to facilitate THN implementation. Policies are typically of two kinds: those that enable naloxone access via broad standing orders, or those that amend Good Samaritan legislation to extend immunity beyond physicians to first responders, bystanders, or witnesses who extend care in emergency situations.

3.3.1.1. United Kingdom In 2005, naloxone was incorporated into the Schedule 7 of the UK Medicines Act which allows any member of the general public to administer naloxone with the aim of saving a life, thereby placing naloxone alongside glucagon, adrenaline and snake antivenin (Strang et al., 2006). Naloxone could then lawfully be given by a witness to an overdose victim to whom it was not prescribed, opening doors to naloxone administration by layperson first-responders. At least 16 sites then implemented THN pilots in England (NTA, 2011). However, naloxone remained a prescription-only medication. Hence the UK Department of Health Orange Guidelines' (DOH, 2007) stated: *"naloxone […] must be prescribed to named patients or supplied to an individual by means of a patient group direction [PGD]."*

3.3.1.2. United States Naloxone is a prescription-only-medication at the federal level, although there is considerable variation due to state-level legislation and lower-court rulings. New Mexico became the first state to remove legal barriers to THN prescribing and distribution in 2001 (Alcorn, 2014) and to grant legal immunity to bystanders via a Good Samaritan law in 2007. New York and Connecticut followed with laws that granted immunity from civil liability to healthcare providers with prescribing authority (Sporer and Kral, 2007).

Established in 2006, the Massachusetts THN pilot program used a standing order to enable public health care workers to provide THN without a prescription (Doe-Simkins et al., 2009). The standing order model allows a lead physician within a given jurisdiction to issue a written order that naloxone can be distributed by designated pharmacists or other qualified professionals (OSF, 2013).

At the end of the 2000s, there were fewer than three dozen THN programs in the US, but the standing order model would lead to a dramatic increase in the following years (OSF, 2013).

3.3.2. First national and state-wide programs

In the late 2000s, first THN programs expanded coverage from a local to a state-wide or national level.

3.3.2.1. Catalonia Following earlier underground distribution of naloxone, the public health agencies of Barcelona and the autonomous region of Catalonia formally launched a THN program in 2008 which allowed staff and clients of participating sites to receive training (EMCDDA, 2016).

3.3.2.2. Scotland Three local pilots were launched in Glasgow, Lanark and Inverness during or after 2007 using the authority of PGDs for nurses and paramedical staff to issue THN (McAuley et al., 2012). In 2011, the Scottish Procurator Fiscal issued a Letter of Comfort , granting immunity to pharmacists who supplied naloxone without prescription to staff working at services with a high rate of overdoses (e.g., hostels) (Angiolini, 2011). These so-called Lord Advocate s guidelines thus permitted naloxone storage in non-medical facilities for emergency use (ACMD, 2012).

The Scottish National Programme was launched in November 2010 (McAuley et al., 2012) and involves THN distribution in the community and to prisoners on release. Services can issue THN to staff, persons at risk of overdose, family members, and peers (with documented consent of the person at risk). The Scottish government funded the program centrally up until 2016. Over the years, the Scottish National Programme would distribute over 20,000 THN kits (McAuley et al., 2017) − approximately 90% in the community and 10% to prisoners on release (ISD, 2016).

3.3.2.3. Wales Following the 2007 introduction of a THN pilot (Bennett and Holloway, 2011, 2012), Wales launched a national naloxone program in 2011. Between mid-2009 and early 2014, 4579 THN kits were issued and reportedly used in 375 overdose events (McDonald et al., 2016).

3.3.2.4. Massachusetts The Massachusetts Department of Public Health has conducted the most comprehensive US program evaluation to date. Boston-based harm reduction activists began THN distribution in the early 2000s without formal approvals and documented the number of naloxone vials distributed and overdose events reversed in a 2005 letter to the mayor of Boston who facilitated a joint meeting between the activists and the Department of Public Health. As a result, Boston Public Health Commission authorized development of a THN program via its mobile needle-exchange scheme in 2006. The Massachusetts THN program was the first to involve distribution of intranasal naloxone and to allow non-medical public health workers to issue naloxone. By 2009, the Massachusetts Department of Public Health had expanded the program to seven more communities, operating out of needle-exchange sites, methadone clinics, homeless shelters, inpatient detoxification programs, community meetings, outpatient and residential addiction-treatment programs, and emergency departments. By 2014, the Massachusetts THN program had trained 4926 drug users, of whom 373 reported administering naloxone (Doe-Simkins et al., 2014).

3.4. 2011–2016 circa: emergence of stronger data, alternative implementation models, and recent efforts to widen naloxone access

By the 2010s intervention studies typically reported the number of overdoses reversed with naloxone as a central outcome; high naloxone usage rates confirmed the trainability of heroin users to adequately respond to overdose (Green et al., 2008; Lopez-Gaston et al., 2009; Markham-Piper et al., 2008; McAuley et al., 2010; Strang et al., 2008a; Tobin et al., 2009; Wagner et al., 2010). A systematic review of naloxone usage rates found that, for every 100 opioid users trained and supplied with THN, 9% of THN kits are likely used for overdose reversal within the first three months post-training (McAuley et al., 2015). However, methodological limitations such as small sample sizes, uncontrolled designs, lack of randomization and systematic follow-up made it difficult to quantify the impact of THN provision on overdose mortality.

3.4.1. A growing evidence base

In 2012, the United Nations Commission on Narcotic Drugs passed Resolution 55/7 (UNODC, 2012), which identified need for more effective prevention of drug overdose, and [e]ncourage[d] all Member States to include effective elements for the prevention and treatment of drug overdose, in particular opioid overdose, in national drug policies, [ ], including the use of opioid receptor antagonists such as naloxone. The same year, the first large-scale randomized trial of THN (N-ALIVE) started recruitment (see Section 3.4.3) (Strang et al., 2013).

In 2013, two cost-effectiveness analyses presented modelling data from the United States and Russia, concluding that THN was cost-effective even when the cost of naloxone increased and the rate of observed overdoses decreased (Coffin and Sullivan, 2013a; Coffin and Sullivan, 2013b). Another 2013 study addressed the impact of THN provision on local overdose rates using an interrupted-time series analysis, finding that Massachusetts-based communities with THN provision had significantly lower overdose mortality rates than communities without (Walley et al., 2013).

Regarding the safety of THN, common concerns were whether THN availability would promote drug use and whether the short half-life of naloxone would result in rebound overdose after the initial dose wore off. A large US retrospective cohort study (n = 4926) concluded that THN provision did not lead to increased heroin use (Doe-Simkins et al., 2014). Previously, a Danish study had found that death from (presumed) rebound overdose toxicity occurred only in 3 out of 3245 cases of naloxone administration (Rudolph et al., 2011).

A waiting-list randomized trial (Williams et al., 2014) of THN training demonstrated good improvements in the knowledge and competence of carers in overdose management, which were maintained at 3-month follow-up − thus confirming the trainability of potential overdose witnesses in the community.

These results were among the key evidence included in a WHO review of community-based naloxone, which led to the November 2014 launch of the WHO Guidelines on the Community Management of Opioid Overdose (WHO, 2014).

The key recommendation was that [p]eople likely to witness an opioid overdose should have access to naloxone and be instructed in its administration (WHO, 2014). Subsequently, a BMJ editorial argued that there is [n]ow enough experience to justify [THN implementation] (Strang et al., 2014).

Following release of the WHO Guidelines, three systematic reviews (Clark et al., 2014; EMCDDA, 2015; McDonald and Strang, 2016) reached similar conclusions. The EMCDDA (2015) concluded: there is evidence that educational and training interventions with provision of take-home naloxone decrease overdose-related mortality (p. 11). Likewise, Clark et al. (2014) found that participation in THN programs led to improved overdose-related knowledge and appropriate use and administration of naloxone. However, the authors (Clark et al., 2014) also reported that the rate of ambulance calls during overdose events was below 50% in 6 out of 9 studies, which appeared to substantiate the concern that THN might discourage users from calling an ambulance. (This concern was later refuted by McAuley et al. (2017) whose interrupted time-series analysis of data

from the Scottish National Naloxone Programme found no association between the supply of take-home naloxone kits and the number of ambulance call-outs). The most recent systematic review (McDonald and Strang, 2016) assessed the safety of THN programs as well as their impact on opioid overdose-related mortality. Evidence from 22 observational studies was evaluated using the nine Bradford Hill criteria (Hill, 1965), devised to assess a potential causal relationship between public health interventions and clinical outcomes when only observational data are available. The analysis confirmed that THN programs met all nine Bradford Hill criteria, reduced overdose mortality among program participants and in the community, and had a low rate of adverse events (McDonald and Strang, 2016).

Finally, in April 2016, the United Nations General Assembly Special Session on Drugs (UNGASS 2016) included naloxone distribution to prevent overdose deaths associated with opioid use as example of evidence-based strategies in its scientific summary (UNODC, 2016a).

3.4.2. Dissemination and expansion

3.4.2.1. Australia Despite immediate endorsement of the original THN proposal by Australian researchers (Darke and Hall, 1997; Fry et al., 2000; Lenton and Hargreaves, 2000), funding for an early naloxone trial in Victoria was affected by the 2000 Australian heroin drought (Dietze, 2016). Intranasal naloxone was explored in ambulance-based trials (Kelly et al., 2005; Kerr et al., 2009), but THN was halted by medico-legal concerns.

Following the emergence of findings from THN schemes overseas, Australian researchers reiterated the case for THN (Dietze and Lenton, 2010; Lenton et al., 2009), which ultimately led to the launch of I-ENNAACT, the first Australian THN program in Canberra, in late 2011.

A preliminary evaluation in late 2014 showed that over 200 injecting drug users had been trained in overdose prevention (including 18 inmates) and reported 57 successful overdose reversals (Dietze, 2016). Naloxone access in Australia was facilitated by the 2012 addition of the antidote to the government Pharmaceutical Benefit Scheme which subsidizes prescription drugs. Australian residents can now obtain naloxone at a concession rate of AUD 5.90, rather than the previous AUD 60 (Fowlie, 2013). The Australian Medical Association endorsed THN in 2013 (Anex, 2013). THN scale-up in New South Wales is currently underway (Dietze, 2016).

3.4.2.2. Continental Europe In the early 2010s, several northern European countries launched THN projects: Denmark and Estonia in 2013, with Norway following in 2014 and Ireland in 2015 (EMCDDA, 2016).

3.4.2.3. United Kingdom In 2012, ACMD urged the Department of Health to review naloxone s prescription-only status (ACMD, 2012). Triggered by this request, the Medicines and Healthcare Products Regulatory Agency (MHRA) released a consultation in 2013, asking for feedback on a proposal to increase community-based naloxone access (MHRA, 2013). Thus, new UK legislation was passed in late 2015 which explicitly enabled wider availability to drug users, family members, other carers, and staff working in relevant treatment and social care agencies. New Public Health England (PHE) guidelines exempted naloxone from the usual prescription requirement when it is supplied by a drug service commissioned by a local authority or NHS (PHE, 2015).

3.4.2.4. United States Amid growing public support, organizations including the US Conference of Mayors, the American Medical Association, the American Public Health Association, and the National Association of Boards of Pharmacy urged states to remove legal barriers to THN (Alcorn, 2014; NPHL, 2016). As of June 2016, forty-eight states had amended laws to relieve provider liability when prescribing or dispensing naloxone, and thirty-seven states had passed Good Samaritan laws (Burris et al., 2001; DOJ, 2014; NPHL, 2014, 2016). Sustainability has been achieved in several states (CDC, 2012).

As of mid-2014, 136 THN programs were providing naloxone kits to laypersons at 644 sites across the country (CDC, 2015), with programs operated by community-based organizations, public health departments, and Veterans Health Administration facilities (Humphreys, 2015). Between 1996 and mid-2014, naloxone kits had been supplied to a total of 152,283 clients who reported 26,463 overdose reversals (CDC, 2015). Among these cases, CRA alone reported training and providing naloxone kits to a total of 36,708 individuals, with 5767 peer overdose reversals (CRA, 2014).

3.4.3. Exploration of new settings and workforces

Community-based harm reduction teams have been the default resource for THN provision, with users and their primary carers the main target populations. The CDC survey (2015) of current THN programs in the US reported that most program participants are people who use drugs (82%), with friends and family members being the second most common group (12%). Over the past five years, researchers have sought to study whether expansion of the THN intervention to new settings and workforces could enhance its impact.

3.4.3.1. Police and firefighters In the US, several jurisdictions have passed legal provisions to authorize nonmedical first responders to administer naloxone (Banta-Green et al., 2013). In 2010, Massachusetts was the first state to pioneer equipping firefighters and police with naloxone (Davis et al., 2014), and the Obama administration s National Drug Control Strategy (ONDCP, 2010) urged training of law enforcement professionals and firefighters in how to recognize an overdose and [in] how to administer [ ] naloxone.

Law enforcement officers can be successfully trained to respond to overdose (Saucier et al., 2016; Wagner et al., 2016).

Over 220 law enforcement agencies across 24 U.S. states carry naloxone (Davis et al., 2015). Equipping Ohio police with naloxone nasal spray was associated with a decline in opioid overdose deaths (Rando et al., 2015). A New York-based program reported over 100 overdose rescues within a year (NYAG, 2015).

Law enforcement officers generally expressed willingness to receive training in overdose management and naloxone administration (Banta-Green et al., 2013; Ray et al., 2015; Wagner et al., 2016). However, a Seattle-based study found law enforcement officers' knowledge of a Good Samaritan law to be low (Banta-Green et al., 2013). Furthermore, training did not impact law enforcement officers' mixed attitudes toward opioid users (Banta-Green et al., 2013; Wagner et al., 2016). Geographical disparities have also been revealed, with naloxone equipment of emergency responders being more common in urban than rural settings (Rando et al., 2015).

3.4.3.2. Primary care Despite extensive contact with opioid users and favorable attitudes towards wider naloxone availability, many providers have remained wary of providing THN (Barry et al., 2017; NPHL, 2014). US primary care providers described insufficient time during patient appointments and inability to follow up with patients as main organizational barriers to THN (Binswanger et al., 2015). Canadian primary care providers considered existing naloxone guidelines inadequate and identified the lack of user-friendly naloxone devices, sufficient funding and training as central barriers to THN provision (Leece et al., 2015). Scottish primary care providers reported low awareness of the national THN program, pointing to their need for training (Matheson et al., 2014).

However, a San Francisco-based project of naloxone co-prescribing for primary care patients receiving long-term opioid pain therapy established that the intervention was feasible, acceptable to patients (Behar et al., 2016) and associated with significantly reduced opioid-

related emergency department (ED) visits at 1-year follow-up (Coffin et al., 2016).

3.4.3.3. Emergency care The Massachusetts THN program provides THN at EDs, and feasibility has recently also been explored elsewhere. A British Columbia survey of ED patients at risk of opioid overdose (Kestler et al., 2017) found that two-thirds accepted THN kits when offered to them at the ED, highlighting the potential of this setting for overdose prevention.

3.4.3.4. Pharmacy-based provision In pharmacy-based THN provision, pharmacists take on a dual role: a) monitoring patients opioid prescriptions and assessing their risk of opioid use disorder as well as b) expansion of naloxone access (Green et al., 2015b; Penm et al., 2017). Since October 2015, UK pharmacies providing supervised opioid substitution treatment can supply THN without prescription to individuals likely to witness an opioid overdose provided the [naloxone] supply is suitably recorded (PHE, 2015). As of August 2016, US pharmacists can prescribe naloxone in 5 states and dispense naloxone via standing orders in forty-two states (Davis and Carr, 2017). Pharmacy-based provision has been piloted as a strategy to promote naloxone access in rural areas (Green et al., 2015b) and increased dramatically in the US since 2013 (Jones et al., 2016). However, pharmacists willingness to dispense THN varies (Freeman et al., 2017) and patients and carers report stigma of THN receipt (Green et al., 2017).

3.4.3.5. Peer-led provision Peer-led naloxone supply is becoming more common. In the UK, (former) service users can be employed or engaged in drug treatment services and supply naloxone to potential overdose witnesses as of October 2015 (PHE, 2015). A Canadian interview study with peer-trainers identified the wish to help others as key motivation and found psychological benefits associated with the peer-trainer role, including a sense of recovery and empowerment (Marshall et al., 2017).

3.4.3.6. Prison release THN provision on prison release was the focus of the N-ALIVE randomized trial in England and Wales, which assessed its impact on overdose mortality in the month post-release (Bird and Hutchinson, 2003; Farrell and Marsden, 2008; Strang et al., 2013). N-ALIVE pilot with its target recruitment of 2800 subjects yielded a marked decrease in opioid-related deaths, a subsequent large-scale trial involving 28,000 prisoners on release was scheduled. However, the pilot was ended prematurely in December 2014 (total enrolment: 1685 subjects) (Parmar et al., 2017) after the SNNP showed a significant reduction in the proportion of opioid-related deaths in the month following prison release. Among Scottish prisoners supplied with THN, mortality decreased to 4.7% by 2013, compared with the pooled 2006 10 baseline of 9.8% (ISD, 2014). Since program start in 2011, heroin-related deaths within 4 weeks of prison release gradually decreased every year, coinciding with a steady increase in the volume of THN kits (Bird et al., 2016; Bird et al., 2015). Prison-based THN has also been introduced and studied in New York City, California, and Rhode Island (Green et al., 2015a; Jordan, 2015; Rosner, 2015).

3.4.4. Efforts to widen availability of naloxone

Since 2015, significant developments have widened naloxone access through a variety of mechanisms, including reformulation of the product.

3.4.4.1. Non-injectable naloxone Naloxone s exclusive availability as formulated for injection is one of the main barriers to wider use, as certain jurisdictions restrict the administration of injections to medical professionals (EMCDDA, 2016). Injectable naloxone is not ideal for layperson use and can present a twofold barrier to THN implementation: on a clinical level, carriage rates for injectable naloxone have been found to be below 20% (McAuley et al., 2016). Laypersons who witness overdose events may be less likely to intervene and administer an injection for lack of familiarity with needle-and-syringe assembly or for fear of needle-stick injury and potential risk of contracting blood-borne diseases (e.g., hepatitis C, HIV) (Wermeling, 2013).

Improvised nasal naloxone kits consisting of a 2 mg/2 ml pre-filled syringe with a nasal mucosal atomizer device were first provided in the Massachusetts THN program in 2005 (Doe-Simkins et al., 2009). Since the prefilled naloxone syringe is approved only for injectable use, the improvised nasal kits represent off-label or off-license use (Strang et al., 2016b). The improvised nasal kits were later introduced elsewhere in the United States, Denmark, Norway, and Scotland s Highland region.

The Norwegian THN program distributed 2056 nasal kits between program start in mid-2014 and late 2015, with 277 overdose reversals reported (Madah-Amiri et al., 2017). The Danish THN kits are unique in that they contain both the mucosal atomizer device for nasal administration and a needle for intramuscular injection in case of non-response to the nasal spray (EMCDDA, 2016).

According to a survey of 136 US-based THN programs, 51% provided only injectable naloxone, 37% provided only improvised nasal kits, and 12% provided both (CDC, 2015).

In 2012, a step-change occurred in the U.S. with the joint initiative of the Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDC), and National Institute on Drug Abuse (NIDA) to encourage new non-injectable naloxone formulations, alongside FDA clarification of the regulatory benchmark: one or multiple doses of any new non-injectable formulation would need result in similar or greater naloxone exposure than the reference product of intramuscular naloxone 0.4 mg (Hertz, 2012). A systematic review identified nasal, buccal and sublingual naloxone delivery as the three viable routes for naloxone administration in an overdose emergency, of which study of the nasal route was most advanced (Strang et al., 2016a).

Prior to the 2012 FDA initiative, only one patent application (WO/2012/156317) for non-injectable naloxone containing human in-vivo data had been filed, highlighting very limited investment from pharmaceutical industry. With injectable naloxone-hydrochloride solution available as generic and off-patent medication, naloxone was of limited commercial value. Moreover, as an antidote, naloxone is only prescribed for emergency use (unlike e.g., medications for opioid substitution therapy), and its per-patient sales volume limited accordingly.

When NIDA announced that it would fund development of user-friendly naloxone delivery systems (Volkow et al., 2014), industry interest finally appeared. Two companies filed separate New Drug Applications for nasal naloxone in 2015, of which only one product was FDA-approved later that year. This concentrated nasal spray product (4 mg/0.1 ml) has a promising pharmacokinetic profile with good bioavailability (Krieter et al., 2016). Whether it can improve community-based naloxone availability remains to be seen.

3.4.4.2. Over-the-counter naloxone Until recently, Italy was the only country where naloxone was available without a prescription. In 1996, the Italian Ministry of Health classified naloxone as an over-the-counter medication, allowing pharmacists to issue naloxone without a prescription (*Senza Obbligo di Prescrizione)* (ForumDroghe, 2016, 2017; Lenton and Hargreaves, 2000; WHO, 2014). However, naloxone cannot be publicly displayed on shelves to which customers have direct access. Customers must request naloxone directly from the pharmacist. While no causal conclusions may be drawn, the 1996 introduction of over-the-counter status was succeeded by a gradual decline in opioid overdose mortality rates in Italy, with 470 deaths in 1999, 280 in 2005, and 101 in 2015 (ForumDroghe, 2016, 2017). As of 2016, 57 Italian harm reduction services distribute THN, but there are stark regional disparities, with services predominantly clustered

in the major metropolitan areas (i.e., Rome, Milan, Bologna, Turin, Naples). Some regions are without THN coverage, which has been linked to the lack of a national harm reduction policy and insufficient investment (ForumDroghe, 2016).

Although THN was only introduced in Australia in 2011, Australia became the second country to have naloxone formally available over-the-counter, following the decision of the Therapeutic Goods Administration to place naloxone when used for the treatment of opioid overdose on Schedule 3, thereby approving over-the-counter (OTC) status (Lenton et al., 2016). Since early 2016, Australian community pharmacists have been able to supply naloxone without a prescription.

In Canada, THN programs exist in seven of the 13 provinces and territories, with large programs in British Columbia (120 sites, 6389 kits distributed) and Ontario (22 sites, 2734 kits distributed) (CCSA, 2016). In 2016, Health Canada approved the previously FDA-licensed nasal naloxone product and issued an interim order to make the spray available without a prescription (CBCnews, 2016).

Select U.S. pharmacies in at least 15 states have special practice agreements allowing pharmacists to sell naloxone (incl. the FDA-approved nasal spray) without a prescription (EMCDDA, 2016). However, it is unclear if or how soon formal re-classification of naloxone from prescription-only medicine to over-the-counter status may occur. An earlier legal analysis suggested this regulatory process might be lengthy and cost-intensive (Burris et al., 2001), as FDA would require additional data demonstrating the ability of laypersons without medical training to correctly diagnose an overdose and administer the formulation (Compton et al., 2013; FDA, 2012).

In the UK, the 2015 PHE guidelines allow people engaged or employed in NHS drug treatment services to make THN available to opioid users, family members, and hostel staff without prescription, provided the naloxone supply is documented accurately (PHE, 2016). Even though naloxone technically remains a prescription-only medication, the guidelines reduce the staffing burden for THN as staff without prescribing authority can issue THN for emergency use.

3.4.4.3. Calls for universal THN provision Beyond lack of funding or political support, low prescriber awareness and commitment persist as central barriers to wider THN access. Despite evidence of effectiveness and endorsements from professional organizations (ACMD, 2000, 2012, 2016; AMA, 2012), many providers fail to integrate THN into standard care for at-risk patients. Dissemination was found to be difficult even among addiction treatment staff (Mayet et al., 2011) with the anticipated cascade of the train-the-trainer-model occurring at the disappointing pace of one drug user trained per clinician trainee in on average 11 months.

Providers struggle with competing clinical demands, making opt-in medical services low priority. A more proactive approach whereby THN was routinely prescribed to all at-risk patients unless patients declined (opt-out system) would likely increase coverage.

An international treatment target similar to the UNAIDS (Joint United Nations Program on HIV/AIDS) 90-90-90 test and treat strategy (introduced to help end the AIDS epidemic) (UNAIDS, 2014) could potentially improve naloxone access in countries affected by opioid-related mortality. Researchers estimate that target naloxone distribution should exceed 100 kits per 100,000 population (Walley et al., 2013) or at least nine times as many naloxone kits as there are annual opioid-related deaths to impact opioid mortality (Bird et al., 2015; Madah-Amiri et al., 2017).

4. Discussion

4.1. Strengths and limitations

This narrative review represents the first peer-reviewed attempt to reconstruct the development of THN from its conception to present.

To allow for the wide scope of this review, a broad search strategy was applied. While the search strategy was not limited to English-language entries, we cannot rule out that relevant international sources (published in other languages) may have been overlooked. Similarly, it is possible that the chronological timeline (see also Table 2) may include inaccuracies.

We present these data as our best estimates that are based on careful extraction from the referenced source documents. We hope to stimulate discussion and invite feedback from take-home naloxone users, advocates, prescribers and researchers around the world.

4.2. Questions for future research

Many questions are still unanswered about THN, including about routes of administration and optimal dose range (especially for overdose from synthetic opioids) (FDA, 2016), and questions on core elements of overdose trainings and their potential impact on behavior. Finally, the question of co-prescription of naloxone for chronic pain patients being treated with opioids is just now being raised (Coffin et al., 2016) as THN research has been largely confined to heroin users.

THN implementation studies have mostly recruited heroin users via urban harm reduction infrastructures, including needle exchange schemes. Implementation studies are needed for emerging target groups such as rural user populations and prescription opioid users (including chronic pain patients) whose overdose risk awareness may be low (Albert et al., 2011; Coffin et al., 2016; Compton and Volkow, 2006; Paulozzi and Ryan, 2006). The US opioid epidemic has led to a demographic shift in heroin users, from urban minority populations to predominantly white suburban and rural men and women (Cicero et al., 2014). Overdose mortality rates (any substance) have increased among men and women of non-Hispanic white and black ethnicity (CDC, 2016). It will be important to examine the demographics of prescription opioid users (including chronic pain patients) in greater detail (Coffin et al., 2016; Ling, 2017; Volkow and McLellan, 2016), particularly considering that the prevalence trends of overdoses from prescription opioids and heroin are likely intertwined and indicative of switching from prescription opioid to heroin use (Unick et al., 2013).

4.2.1. Models for implementation

Implementation research will be necessary as THN programs move into new settings. One such feasibility study is currently being undertaken in correctional and reentry settings in California, where stakeholder interviews and focus groups are being conducted to address THN implementation barriers (NIH project number: 5R34DA039101-02).

Research is also needed to systematically compare different settings and distribution models for THN to identify those with biggest reach among target populations. The issue of THN cost also needs to be considered. For instance, it is unknown how likely potential overdose witnesses are to access and obtain naloxone via THN programs at no cost versus as over-the-counter medication for sale. Availability of naloxone solely over-the-counter, i.e., without additional free distribution, may only yield limited community-based coverage. Such is the case in Italy, where naloxone was reclassified to over-the-counter medication in 1996, but some regions remain without community-

based naloxone coverage, presumably because of insufficient public investment (ForumDroghe, 2016).

By analogy, in the prevention of sexually transmitted infections (STIs), a systematic review identified cost as barrier to condom use (Ubrihien et al., 2016). Consequently, recent NICE guidelines recommend free-of-charge condom distribution schemes to target populations at highest risk of STIs (Iacobucci, 2017; NICE, 2017).

4.2.2. Naloxone coverage

Future studies will need to look at the extent to which widespread THN provision, as perhaps achieved in Scotland (Bird et al., 2017; McAuley et al., 2017), Norway (Madah-Amiri et al., 2017) and several states in the US (Walley et al., 2013), results in reduction in opioid overdose mortaliy at state or national level, and what naloxone coverage rates are required to achieve this effect.

4.2.3. Opioid user engagement

Despite increasing THN provision among (recent) injecting drug users from 8% (2006 10 baseline) to 51% (2014 2015) (Bird et al., 2017), the Scottish National Naloxone Programme reported naloxone carriage rates of only 5 16% (McAuley et al., 2016), highlighting the need to improve user engagement in take-home programs.

Qualitative research may help shed light onto barriers to THN intervention uptake. While opioid users in Baltimore and Chicago reported predominantly positive interactions with police and paramedics (Sherman et al., 2008) and expressed interest in THN provision as well as willingness to share information on overdose emergency management with peers and family members (Sherman et al., 2009), naloxone experiences likely differ. Qualitative interviews conducted in Scottish cities in 1997 99 (Neale and Strang, 2015) revealed opiate users negative views of naloxone and accounts of harm caused by its administration (e.g., acute withdrawal, aggression, self-discharge and further drug-seeking), even though this was not apparent in observational data.

Similarly, opioid users in New York and Los Angeles reported fear of withdrawal and police involvement as key concerns associated with THN distribution (Lankenau et al., 2013; Worthington et al., 2006), and continued use of folk remedies posed a barrier to THN use (Lankenau et al., 2013).

Systematic study of lived naloxone experiences is needed to identify strategies for increasing user engagement in THN programs.

5. Conclusion

Twenty years ago, the very idea of THN was a radical speculative proposal to extend harm reduction beyond needle and syringe exchange. Today THN is increasingly accepted as an effective public health strategy to reduce overdose fatalities and is increasingly being considered as part of routine care and possibly a required standard of care. Nonetheless, THN lags behind its full potential, with only modest distribution of THN relative to the evident (and growing) clinical need. To date, THN distribution has mostly been made possible by community-based harm reduction organizations with limited central funding. To tackle the rising numbers of opioid-related deaths, governments will need to provide political leadership and perhaps specific financial support to improve the necessary extent of coverage of this potentially life-saving intervention.

Contributors

JS, NC and RM drafted the manuscript. RM conducted the literature search. All authors approved of the final draft of the manuscript.

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No specific funding was sought or secured for the review reported in this paper.

Conflict of interest

JS declares that he is a researcher and clinician who has worked with a range of types of treatment and rehabilitation service-providers. JS is an NIHR Senior Investigator and is also supported by the National Institute for Health Research (NIHR) Biomedical Research Centre for Mental Health at South London and Maudsley NHS Foundation Trust and King s College London. He has also worked with a range of governmental and non-governmental organizations, and with pharmaceutical companies to seek to identify new or improved treatments (including naloxone products) from whom he and his employer (King s College London) have received honoraria, travel costs and/or consultancy payments. This includes work with, during past 3 years, Martindale, Indivior, Mundipharma, Braeburn and trial medication supply from iGen and Braeburn. JS has been named as an inventor in a patent application for concentrated naloxone nasal spray. For fuller account, see www.kcl.ac.uk/ioppn/depts/addictions/people/hod.aspx.

RM has undertaken an unpaid student industry placement with Mundipharma Research Ltd., with focus on the analysis of naloxone nasal spray formulations.

King s College London (employer for both JS and RM) has separately applied to register intellectual property on a novel buccal naloxone formulation with which JS and RM are involved.

RM and JS are working as consultants for the United Nations Office on Drugs and Crime (UNODC), supporting a feasibility study of community-based opioid overdose prevention strategies in the framework of the UNODC-WHO Programme on Drug Dependence Treatment and Care (GLOK32). The views expressed in this article are those of the authors and do not necessarily reflect the position of the United Nations.

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ADDICTION

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REVIEW

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Are take-home naloxone programmes effective? Systematic review utilizing application of the Bradford Hill criteria

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ABSTRACT

Background and Aims Fatal outcome of opioid overdose, once detected, is preventable through timely administration of the antidote naloxone. Take-home naloxone provision directly to opioid users for emergency use has been implemented recently in more than 15 countries worldwide, albeit mainly as pilot schemes and without formal evaluation. This systematic review assesses the effectiveness of take-home naloxone, with two specific aims: (1) to study the impact of take-home naloxone distribution on overdose-related mortality; and (2) to assess the safety of take-home naloxone in terms of adverse events. **Methods** PubMed, MEDLINE and PsychINFO were searched for English-language peer-reviewed publications (randomized or observational trials) using the Boolean search query: (opioid OR opiate) AND overdose AND prevention. Evidence was evaluated using the nine Bradford Hill criteria for causation, devised to assess a potential causal relationship between public health interventions and clinical outcomes when only observational data are available. **Results** A total of 1397 records (1164 after removal of duplicates) were retrieved, with 22 observational studies meeting eligibility criteria. Due to variability in size and quality of the included studies, meta-analysis was dismissed in favour of narrative synthesis. From eligible studies, we found take-home naloxone met all nine Bradford Hill criteria. The additional five World Health Organization criteria were all either met partially (two) or fully (three). Even with take-home naloxone administration, fatal outcome was reported in one in 123 overdose cases (0.8%; 95% confidence interval = 0.4, 1.2). **Conclusions** Take-home naloxone programmes are found to reduce overdose mortality among programme participants and in the community and have a low rate of adverse events.

Keywords Bradford Hill, death, heroin, naloxone, opiate, opioid, overdose, prevention.

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INTRODUCTION

Opioid overdose represents a major cause of premature death [1] and accounts for the majority of deaths among injection drug users (IDUs) world-wide [2]. Opioid overdose deaths are preventable through timely administration of naloxone, a potent mu-opiate antagonist that rapidly reverses opiate-induced respiratory depression.

In 2014, the World Health Organization (WHO) launched guidelines on the community management of opioid overdose [3], recommending that 'people likely to witness an opioid overdose should have access to naloxone and be instructed in its administration' (p. x).

The community-based provision of naloxone rescue kits to opioid users ('take-home naloxone', THN) was first proposed in the 1990s [4]. THN programmes typically involve training opioid users and/or their family members or peers in overdose risk awareness, overdose emergency management and naloxone administration [5]. During the past 15 years, THN programmes have been implemented in Europe, North America, Asia and Australia [1]. However, the vast majority of evaluations have been pilot schemes with uncontrolled study designs.

The evaluation of THN programmes is challenging: randomized controlled trials (RCTs) are often considered the gold standard of scientific study of clinical impact, but conducting such trials in this context would often be unethical and fraught with methodological difficulties, given the infrequency and unpredictability of overdose.

Critics of THN programmes argue that the existing observational data are not strong enough to infer causation from naloxone provision to the reduction of overdose deaths [6,7]. A counter-argument may be that similar reservations initially blocked other harm reduction strategies, including needle exchange programmes and opioid substitution therapy [8] that are now evidence-based practice [9] (and would still be absent if the precautionary principle had been strictly applied).

A clearer understanding of the potential benefits and risks of THN provision is essential. If concerns are valid they need to be identified and considered in context, but mere assertions of hypothetical disadvantages must not prohibit access to a life-saving medication. A previous systematic review [10] found that participation in THN programmes led to improved overdose-related knowledge as well as appropriate use and administration of naloxone, but the impact on overdose mortality was not assessed.

Our goal in this review is to assess the effectiveness of THN programmes by following a well-recognized process (i.e. Bradford Hill criteria) rigorously to evaluate the data within eligible studies, addressing the following two aims: (1) to describe the impact of THN provision on overdose-related mortality in opioid users; and (2) to assess the safety of THN provision by quantifying adverse events associated with naloxone administration.

METHODS

A systematic literature search was performed following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidance (see Fig. 1 for PRISMA flow diagram and Supporting information, Appendix S1 for search protocol and excluded studies).

Identification of eligible studies

Electronic databases were searched to identify relevant peer-reviewed papers published between January 1946 and June (third week) 2015. Replicating the search strategy reported by Clark *et al.* [10], the following Boolean search query was used: (opioid OR opiate) AND overdose AND prevention.

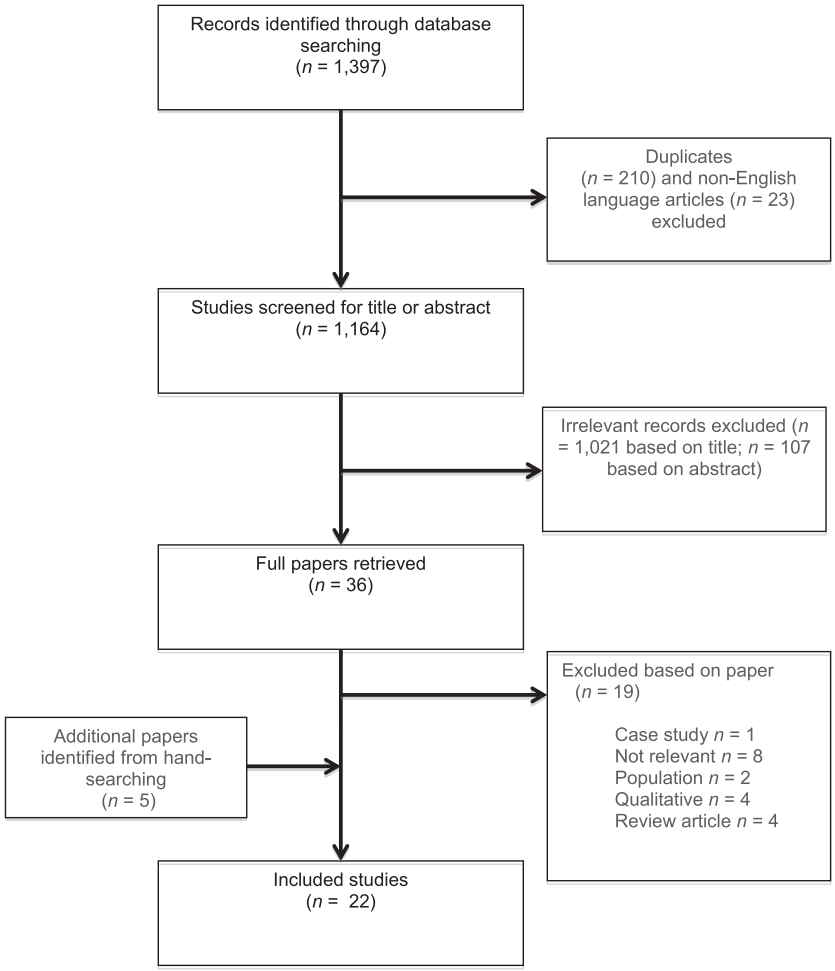

Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of study selection process

Electronic database searching generated 1397 records: 150 on Medline, 772 on PsycInfo (both via OVID) and 475 on PubMed. Five studies [11–15] were added after a manual search of the reference lists of recent literature reviews [10,16,17].

Original quantitative (or mixed-method) studies of randomized or observational trials of THN programmes that trained opioid users in overdose prevention AND reported on overdose outcomes were included into the study. Several exclusion criteria were applied: reporting on buprenorphine/naloxone; case reports; not reporting primary research data; not reporting on heroin/opioid users, naloxone or overdose.

Under supervision of the senior investigator, the first author extracted data using the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist [18], assessed study eligibility and conducted quality appraisal using an eight-item scale by Jinks *et al.* [19], which had been applied previously by Clark *et al.* [10] (see Table 4).

All 22 studies that met the inclusion criteria were entered into the analysis. Among these, one was an interrupted time–series analysis that provided quasi-experimental data. Sixteen were pre–post studies (nine with systematic follow-up), three were case series and two were cross-sectional. None of the studies involved randomization to the intervention (i.e. THN distribution), although two studies were controlled [12,20]. Of the 22 included studies, 15 were carried out in the United States, two in Canada, four in the United Kingdom and one in the United Kingdom and Germany (multi-site). Sample sizes varied from a minimum of 24 to a maximum of 2912 (median: $n = 203$).

Analysis

There was large variability in the size and quality of the THN intervention studies identified: for example, many were merely descriptive reports which, while valuable communications to other practitioners, were nevertheless lacking study design or analytical rigour. Moreover, while nine studies involved systematic follow-up, they were not considered necessarily representative of the majority of included studies due to small sample sizes. As a consequence, narrative synthesis was chosen as the more appropriate method of analysis in lieu of meta-analysis.

In this context, the evidence was evaluated using the Bradford Hill criteria [21], a set of nine criteria (see Table 1) devised in 1965 by British epidemiologist and statistician Sir Austin Bradford Hill to assess causality when only correlational data are available: (1) strength of association, (2) consistency, (3) specificity, (4) temporality, (5) dose–response relationship, (6) plausibility, (7) coherence, (8) experimental evidence and (9) analogy. The Bradford Hill criteria are considered a standard tool to assess the impact of broad-based public health interventions where it is not ethically feasible or operationally impractical to conduct RCTs.

The Bradford Hill criteria have been applied valuably in a WHO 'Evidence for Action' report [22] on the effectiveness of needle-exchange interventions in reducing HIV among IDUs. The WHO report also considered evidence according to five additional criteria relating to feasibility and implementation (see Table 2), which we include as supplementary analysis: (10) cost-effectiveness; (11) absence of negative consequences; (12) feasibility of implementation, expansion and coverage; (13) unanticipated benefits; and (14) special populations.

Where summary outcome measures (e.g. number of naloxone administrations, overdose reversals, adverse events) were calculated across studies, we sought to avoid (partial) duplication of samples by including only the study with the largest participant sample per project [20,23] for THN projects that had produced more than one published study (i.e. Boston/Massachusetts, Los Angeles, New York, San Francisco). Vice versa, if the time-periods covered by multiple studies from the same project could be distinguished clearly and did not overlap, all project evaluations entered analysis [24–27]. All summary statistics are pooled, unweighted estimates from the referenced studies. The number of overdose reversals is used as proxy for the impact of THN provision on opioid overdose mortality (aim 1), as a ratio of one fatal overdose in every 20 overdose events has been described in the literature [28], and it is impossible to ascertain for each overdose event whether, in the absence of intervention, the outcome would have been fatal or whether respiratory function would have recovered.

RESULTS

We now present the findings from application of the nine original Bradford Hill criteria [21], followed by consideration of the extra five criteria added in the WHO report [22,29].

Consideration according to the original Bradford Hill criteria

Strength of association

In 21 of the 22 studies, pre-provision of naloxone was followed by use of the naloxone to reverse opioid overdose. After exclusion of four studies that possibly contained duplicate samples [30–33], a total of 2336 THN administrations were found across 17 studies (see Table 3). Due the

Table 1 Bradford Hill criteria: definition and application to take-home naloxone.

Criterion	*Definition*	*Take-home naloxone (THN)*
Strength of association	The stronger the association between the exposure to a treatment and the clinical outcome, the less likely it is influenced by an external variable	How strong is the association between THN and overdose (OD) reversal?
Temporality	A cause-and-effect hypothesis can only find empirical support if the presumed cause precedes the effect in time	Did the distribution of THN precede a reduction in OD deaths?
Consistency	The credibility of a finding increases if different investigators can replicate it across different locations and under different circumstances	Have there been multiple observations of OD reversals as a result of THN provision?
Biological plausibility	There is stronger support for causality if there is a likely biological or pharmacological mechanism that can explain the association between exposure to a treatment and the outcome	Is it biologically plausible that a reduction in OD deaths occurs when THN is available?
Coherence	Causality between a treatment and outcome is supported when the association is coherent with current knowledge of the disease. Vice versa, conflicting or lack of supporting evidence would count against coherence	Are there documented examples of opioid OD mortality declining without THN availability? If so, does this empirical evidence conflict with the assumed association between THN and OD prevention?
Specificity	Causality can be established when one intervention leads to one specific outcome	Does THN have the unique effect of reversing opioid ODs?
Dose–response relationship	If a dose–response relationship can be observed for the cause-and-effect hypothesis, increased exposure to treatment will proportionally impact the clinical outcome	Does increased THN supply go hand-in-hand with more OD reversals?
Experimental evidence	If experimental manipulation of the exposure–outcome association impacts the outcome, (semi)experimental evidence is given. This delivers the strongest support for causation	Is there (semi)experimental evidence to support the hypothesized impact of THN on OD mortality?
Analogy	If a treatment/exposure factor similar to A leads to a clinical outcome similar to B, then this analogy counts as evidence in support of our hypothesis that A causes B	Is there a treatment similar to THN that leads to an outcome similar to OD reversal?

Table 2 Additional feasibility and implementation criteria and application to take-home naloxone.

Criterion	*Take-home naloxone (THN)*
Cost-effectiveness	Is THN for lay overdose reversal cost-effective compared to treatment as usual (no intervention)?
Absence of negative consequences	Does the distribution of THN to users bear the risk of adverse events?
Feasibility of implementation, expansion, and coverage	Is it feasible to introduce THN distribution in diverse settings, including resource-poor settings, and scale up implementation?
Unanticipated benefits	Does the distribution of THN to users lead to unanticipated benefits?
Special populations	How successful are THN programmes in reaching special populations that have been identified as particularly 'at-risk' opioid users?

Table 3 Included studies: naloxone kits distributed and used, overdose reversals and adverse events.

Study	*n*	*THN kits distributed*	*THN kits used (%)*	*Deaths*	*OD reversal after THN* [e]	*Unknown outcomes*	*Adverse reactions*
Bennett 2011	426	426	249 (58%)	2	≥ 96%	8	NR
Bennet 2012	525	NR	28 (NR)	1	96%		NR
Dettmer 2001[f]	101	101	5 (5%)	0	100%		Withdrawal (NR)
Dettmer 2001[f]	124	124	29 (23%)	0	100%		Withdrawal (10)
Doe-Simkins 2009[d]	385	385	74 (19%)	0	100%		Withdrawal (2)
Dwyer 2015[d]	415	56	6 (11%)	0	100%		NR
Enteen 2010	1942	2962	399 (13%)	6	≥ 89%	36	Vomiting (50), agitation (36), seizures (3)
Galea 2006	25	25	10 (40%)	1[a]	100%	1[a]	None
Lankenau 2013[d]	30	30	15 (50%)	0	≥ 97%	1	NR
Leece 2013	209	209	17 (8%)	0	100%		None
Lopez-Gaston 2009	70	70	0 (0%)	1[a]	NA		NA
Markham Piper 2008	122	122	82 (67%)	0	≥ 83%	14	NR
Maxwell 2006	1120	3500	319 (9%)	1[c]	99%		Seizures (1), vomiting (1)
McAuley 2010	41	19	2 (11%)	1[a]	100%		NR
Rowe 2015	2500	2500	702 (28%)	10	99%		NR
Seal 2005	24	24	15 (63%)	0	100%		NR
Strang 2008	239	239	1 (5%)	1[a]	100%		Withdrawal
Tobin 2009	250	250	22 (9%)	0	100%		NR
Tzemis 2014	692	836	85 (10%)	0	100%		Withdrawal (55), agitation (9)
Wagner 2009	66	66	28 (42%)	4[b]	NR	5	Agitation (5), vomiting (1)
Walley 2013 [20]	2912	2912	327 (11%)	0	100%		NR
Walley 2013 [33][d]	1553	1553	92 (6%)	0	100%		NR
Yokell 2011	120	120	5 (4%)	0	100%		NR

[a]Naloxone not administered; [b]unclear if naloxone administered; [c]non-opioids present; NA: not applicable; NR: not reported; OD = overdose; THN: take-home naloxone; [d]not included in summary measures to avoid (partial) duplication of samples; [e]where applicable, unknown outcomes were counted towards unsuccessful THN administrations (as indicated by the ≥ symbol); [f]Multi-site study with two samples: Jersey (n=101) and Berlin (n=124).

binary outcome (survival/death), the number of successful overdose reversals can be estimated by deducting the number of deaths from the number of THN administrations. By deducting the 20 confirmed deaths (1 + 1 + 2 + 6 + 10) where overdose victims did not recover following naloxone administration [12,24,25,34,35], we obtain an upper estimate of 2316 successful overdose reversals.[1] If the four deaths where it was unclear if naloxone had been administered [23] and 63 cases (8 + 36 + 14 + 5) of naloxone administration with 'unknown outcome' [23,24,27,34] are

[1]2316 overdose (OD) reversals = 2336 THN administrations minus 20 deaths (see Table 3).

Table 4 Included studies: follow-up rate, study design and quality rating.

Study	*Location*	*n*	*FU*	*FU %*	*FU type*	*Design*	*Score*
Bennett 2011	Pittsburg	426	89	21%	Non-systematic	Pre–post	5
Bennet 2012	Wales	525	28	5%	Systematic	Pre–post	6
Dettmer 2001[a]	Jersey	101	NR	NR	Non-systematic	Case series	4
Dettmer 2001[a]	Berlin	124	40	32%	Non-systematic	Case series	4
Doe-Simkins 2009	Boston	385	278	72%	Non-systematic	Pre–post	5
Dwyer 2015	Boston	415	51	12%	Systematic	Pre–post	6
Enteen 2010	San Francisco	1942	310	16%	Non-systematic	Pre–post	6
Galea 2006	New York	25	22	88%	Systematic	Pre–post	7
Lankenau 2013	Los Angeles	30	NA	NA	NA	Cross-sectional	6
Leece 2013	Toronto	209	NR	NR	Non-systematic	Case series	5
Lopez-Gaston 2009	Birmingham & London	70	46	65%	systematic	Pre–post	7
Markham Piper 2008	New York	122	NR	NR	Non-systematic	Pre–post	6
Maxwell 2006	Chicago	1120	NR	NR	Non-systematic	Case series	4
McAuley 2010	Lanarkshire	41	17	89%	Systematic	Pre–post	7
Rowe 2015	San Francisco	2500	613	25%	Non-systematic	Pre–post	7
Seal 2005	San Francisco	24	24	100%	Systematic	Pre–post	5
Strang 2008	England	239	186	78%	Systematic	Pre–post	7
Tobin 2009	Baltimore	250	85	34%	Systematic	Pre–post	6
Tzemis 2014	British Columbia	692	NA	NA	NA	Cross-sectional	6
Wagner 2009	Los Angeles	66	47	71%	Systematic	Pre–post	7
Walley 2013 [20]	Massachusetts	2912	212	7%	Non-systematic	ITS	7
Walley 2013 [33]	Massachusetts	1553	286	18%	Non-systematic	Pre–post	6
Yokell 2011	Rhode Island	120	10	8%	Non-systematic	Pre–post	5

FU: number of follow-up participants; FU%: FU participants as percentage of study sample; ITS: interrupted time–series analysis; NA: not applicable; NR: not reported; score: summary quality score based on eight-point scale by Jinks *et al.* [19], modified from Clark *et al.* [10] [a]Multi-site study with two samples (Jersey, Berlin).

also counted towards fatalities following naloxone administration, a conservative, lower estimate of 2249 successful overdose reversals[2] emerges. In the only study where THN provision did not lead to overdose reversals [11], nine of 46 programme participants witnessed a total of 16 overdoses at 6-month follow-up, but none administered naloxone to the overdose victims. The main reason for non-administration was that participants did not have their naloxone supply available.

In summary, there is a strong association between THN programmes and overdose survival, as evidenced by at least 2249 successful overdose reversals [96.3%; 95% confidence interval (CI) = 95.5, 97.1] among 2336 THN administrations.

Temporality

In 21 of the 22 studies, training in overdose prevention and THN provision preceded overdose reversals. Two of these studies provide clear evidence in support of the temporality criterion. Supportive evidence comes from descriptive accounts of early THN distribution in Chicago and surrounding Cooks County [35]: after a 135% increase in local overdose deaths from 1996 to 2000, the introduction of THN in 2001 led to reduction in fatal overdoses by 20% in 2001, 8% in 2002 and 6% in 2003 (compared to past-year rate). While these data are indicative of a temporal sequence between THN introduction and reduced overdose mortality, no definite conclusion can be drawn, as the lack of control group means that other causes may have contributed to decreasing overdose mortality rates.

Stronger evidence comes from Walley *et al.* [20] who conducted an evaluation of a state-funded THN programme in Massachusetts. Between 2006 and 2009, the Massachusetts Department of Public Health used a phased roll-out to introduce THN in 19 communities, enrolling 2912 individuals in total. To evaluate the impact of THN, Walley *et al.* used an interrupted time–series analysis, where each community served as its own geographic control and communities without concurrent THN availability served as time control. For all 19 participating communities, overdose mortality rates in the time-periods before and after THN implementation were compared. Overdose mortality rates were reduced significantly in communities where THN was implemented, compared to pre-implementation rates and to communities without THN.

Consistency

Overdose reversals by means of THN have been documented in the selected studies by independent investigators

[2]2249 overdose (OD) reversals = 2336 THN administrations minus 20 deaths minus four unclear cases minus 63 cases with unknown outcome.

under different circumstances in at least 15 different cities, states and countries: in Canada (Toronto and British Columbia), the United States (Baltimore, Boston/Massachusetts, Chicago, Los Angeles, San Francisco, New York, Pittsburgh, Rhode Island), the United Kingdom (England, Jersey, Scotland, Wales) and Germany (Berlin). Overdose reversals by THN have also been documented repeatedly in New York [26,27] and San Francisco [14,24,25]. In conclusion, there is substantial support for the consistency criterion.

Biological plausibility

This criterion addresses the therapeutic effect of naloxone. Naloxone is a pure opioid antagonist that binds to the μ-opioid receptor and blocks competing agonists, such as heroin [36]. All but one study [11] reported on THN administration in cases of suspected opioid overdoses, and the pharmacological effects of naloxone led to at least 2249 overdose reversals. In conclusion, there is strong empirical support to the biological plausibility criterion.

Coherence

Declining overdose rates in the absence of THN have been reported in the literature. The Australian heroin drought constitutes a prominent example, where between 2001 and 2002 overdose-related mortality rates dropped in conjunction with a shortage in illicit heroin imports. THN could not have accounted for the decline in mortality, as it was introduced in Australia only in 2011 [37,38]. However, the Australian example does not conflict with the presumed effect of THN on reduced overdose mortality. The cause-and-effect interpretation of our data is consistent with current understanding of the mechanisms of opioid overdose, and the 21 studies which reported overdose reversals provide strong support for the coherence criterion.

Specificity

The specificity criterion relates to efficacy of the intervention (the same as biological plausibility), rather than population-wide effectiveness. THN exclusively reverses opioid-induced overdoses, as illustrated by the following two cases: in the Dettmer *et al.* study [39], naloxone had zero effect when administered to a person suffering from cocaine intoxication. The Chicago Recovery Alliance reported one fatality after naloxone administration [35] where naloxone failed to revive an overdose victim with non-opioids in their system. The mooted benefit from naloxone is specific to opioid overdose. In practice, THN may be primarily beneficial for the reversal of overdoses from heroin and other short-acting opioids. (All 22 studies reported primarily on heroin overdoses, and one study specified that the long-acting opioid methadone was involved in less than 5% of overdose reversals [33].) Overall, the evidence constitutes strong support for this criterion.

Dose–response relationship

Researchers estimate that THN distribution can only achieve maximum impact on overdose reduction if a certain volume of THN kits is available in the community. Among the 22 studies, only Walley *et al.* [20] assessed the impact of varying degrees of THN availability on overdose mortality by splitting the 19 participating communities into three groups based on volume of THN distribution: zero implementation, low implementation (1–100 programme enrolments per 100 000 inhabitants) and high implementation (>100 enrolments). Both low and high implementers had significantly reduced overdose mortality rates compared to communities without implementation, and there was a significant implementation dose-relationship with overdose death rates, with greatest effect with greatest implementation.

To summarize, there is only this limited empirical evidence for a dose-related impact of THN availability, and hence this criterion is only partially fulfilled.

Experimental evidence

While none of the 22 studies deliver experimental evidence, the interrupted time–series analysis by Walley *et al.* [20] provides quasi-experimental evidence in support of causation. Importantly, even communities with low-level THN implementation of THN (1–100 participants, see above) saw a reduction in overdose mortality, compared to communities without THN distribution. Interrupted time–series analysis is considered to be the strongest quasi-experimental research design [40]. The results of the study by Walley *et al.* [20] thus provide preliminary support for the experimental evidence criterion.

Analogy

THN is analogous to naloxone treatment for the same clinical indication in emergency medical care, and also to the prescription of other emergency medications (typically antidotes for overdose or poisoning) for peer administration: THN has been compared to the provision of adrenaline injection kits (e.g. EpiPen) to individuals with severe allergic reactions for family members to administer in the event of anaphylactic shock [15] or the provision of glucagon for insulin overdose [35]. Similarly, THN has been likened to pre-placement of defibrillators and cardiopulmonary resuscitation (CPR) training for lay people likely to witness cardiac arrest [41]. For all these emergency interventions, timely delivery is crucial. We conclude that the analogy criterion is fulfilled.

Consideration according to additional feasibility and implementation criteria

Cost-effectiveness

Separate modelling data from both the United States and Russia conclude that THN is cost-effective even under conservative circumstances, i.e. when the cost of naloxone increases and the rate of observed overdoses decreases [42,43]. Bearing in mind the potential limitation that both studies were conducted by the same authors, there is consistent evidence for the cost-effectiveness of THN.

Absence of negative consequences

In five of the 17 studies that did not contain duplicate samples, 20 overdose victims did not survive naloxone administration [12,24,25,34,35]. In addition, Wagner *et al.* [23] reported four deaths where it was unclear if naloxone had been administered. Based on these observations, the following fatality rates emerge: 20 confirmed deaths per 2336 naloxone administrations (0.9%; 95% CI = 0.5, 1.2) or 24 deaths per 2336 naloxone administrations (1.0%; 95% CI = 0.6, 1.4) if we include the four fatalities where it was unclear if naloxone had been administered. If we limit the study selection to the nine papers with systematic follow-up, a similar ratio of one confirmed death per 123 naloxone administrations (0.8%; 95% CI = 0.4, 1.2) was observed.

In six [15,23,24,35,39,44] of the 17 studies, several adverse reactions were reported in conjunction with a total of 2336 naloxone administrations: at least 65 instances of withdrawal symptoms (2.8%), 52 cases of vomiting (2.2%), 50 cases of agitation (2.1%) and four seizures (0.1%).

In conclusion, THN programmes have a low rate of adverse events. Where adverse reactions occurred, these were most frequently symptoms of opioid withdrawal (including nausea/vomiting, agitation).

Feasibility of implementation, expansion and coverage

The 22 studies document THN implementation in a variety of settings across 16 geographical locations, and naloxone usage rates between 5 and 63% are reported. San Francisco is an example of rapid expansion, as the volume of THN kits distributed increased from 24 in 2001 to 2962 kits during the 6-year period between 2003 and 2009 (i.e. approximately 494 kits/year) [24], and to 2500 kits from 2010 to 2013 (i.e. approximately 833 kits/year) [25]. Outside the 22 studies included in this review, implementation in resource-poor settings has been achieved in Kyrgyzstan and Tajikistan, with reported naloxone usage rates of 47 and 78%, respectively [45]. These studies suggest that THN schemes are capable of implementation across a wide range of settings and cultures.

Unanticipated benefits

Four of the 22 studies reported unanticipated benefits. In THN programmes in California, 25% of participants in San Francisco entered treatment within 6-month follow-up [14] and 53% of participants in Los Angeles reported decreased drug use at 3-month follow-up [23]. Similarly, Maxwell *et al.* reported anecdotal evidence of increased willingness among THN recipients to be tested for HIV and hepatitis C virus (HCV) [35]. Strang *et al.* [15] found a secondary training effect: within a 3-month follow-up period, 28% of THN recipients had trained a family member or peer.

Special populations

THN provision has been implemented successfully in programmes targeting special populations with high risk of overdose: detox patients [11,33], homeless users [23–25,27,46], methadone patients [33] and prison inmates [12]. The Massachusetts THN programme [20] also enrolled attendees of HIV education centers, and a Los Angeles-based programme recruited more than 50% HCV-positive patients. Both represent particularly vulnerable groups due to their comorbid health issues and risk of blood-borne virus transmission by needle-sharing. From the perspective of implementation, THN schemes can be delivered to populations in special need.

Summary of findings

Empirical evidence from the 22 studies reporting on THN interventions for opioid users meets all nine Bradford Hill original criteria. Among these, Sir Austin Bradford Hill considered the experimental evidence criterion to deliver the strongest support for causation [21], but only quasi-experimental evidence from one study [20] is available here. The robustness of empirical support ranges from one study per criterion (dose–response, experimental evidence) to 21 studies per criterion (strength of association, coherence) (see Supporting information, Appendix S1). With regard to the five additional criteria assessing feasibility and implementation, THN fulfils fully or partially all five criteria. It is found to be cost-effective, and existing projects were able to access and train high-risk populations that led to 2336 layperson naloxone administrations (aim 1) with a low rate of adverse effects (aim 2).

DISCUSSION

Application of the Bradford Hill criteria to the current evidence base on THN supports the causation hypothesis. While the evidence is sometimes based on only one or two studies, we nevertheless conclude that this constitutes support for all nine criteria. THN provision reduced fatal

outcome of overdose among programme participants themselves, among fellow opioid users and in the wider community, as evidenced by public vital statistics records [14,20]. Alternative explanations for this observation are unlikely: in control communities that did not implement THN, opioid overdose mortality was significantly higher [20]. The risk associated with THN programmes is relatively low, especially when the life-threatening nature of the emergency situation is borne in mind: in studies with systematic follow-up, one death was reported among 123 overdose victims who were administered THN. Moreover, there is no empirical evidence to support the concern that THN programmes might encourage heroin use. Two studies reported decreased drug use among THN programme participants at follow-up [14,23], whereas a more recent study found no overall change in the frequency of heroin use across THN recipients [47].

This is the first published application of the Bradford Hill criteria to assess the international evidence base on THN. Our findings extend and substantiate the 2014 WHO Guidelines as well as the results of the previous systematic reviews by Clark *et al.* [10] and the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) [17]. Clark *et al.* (2014) cautiously concluded: 'participation [in THN programs] is associated with overdose reversals' (p. 162), but avoided statements on the effectiveness of THN, whereas the EMCDDA stated: 'there is evidence that educational and training interventions with provision of take-home naloxone decrease overdose-related mortality' (p. 11).

There are potential limitations to this analysis, which need to be borne in mind. Selection bias may have affected the internal validity of the data included. Among 19 studies with pre–post and case series designs, 10 relied on unsystematic follow-up to capture overdose events and naloxone usage, relying upon spontaneous follow-up, with THN programme participants asked typically to report back on naloxone usage when collecting a naloxone refill. This raises scientific analytical doubt about data quality and interpretations: first, across these 10 studies, fewer than a quarter (22.9%; i.e. 1973 of 8602) of THN recipients returned for refills after THN use, and information on the majority of participants was consequently lost. Secondly, it is possible that users with positive naloxone experiences (e.g. successful overdose reversals) may be more likely to return for a refill of their THN kit and complete a follow-up survey, whereas those with negative naloxone experiences may not be captured in the follow-up. The lack of systematic follow-up in the majority of studies is reflected in the wide range of follow-up rates attained across all studies (min. 5%, max. 100%). High levels of dropout can reduce the external validity and generalizability of results. A further source of potential bias lies in the fact that, for 21 of the 22 studies, there was an exclusive reliance on self-report data for overdose outcomes. Only the interrupted time–series analysis by Walley *et al.* [20] included a public database of vital statistics to calculate overdose fatality rates. A further limitation concerns the fact that the experimental evidence and dose–response criteria hinge on data from the Walley *et al.* [20] study. More well-conducted studies are needed to confirm these results and assess their applicability to other regions internationally, in particular low- and middle-income countries. Moreover, the findings from the studies do not inform which distribution model of overdose education and THN distribution is preferable. Future studies could evaluate the impact of programme components formally by providing THN to all subjects and randomizing subjects into different training conditions (e.g. 'overdose education' versus 'overdose education + CPR training').

Despite these methodological limitations, positive reports of overdose reversals following THN distribution were reported across 21 studies, regardless of type of follow-up (systematic versus unsystematic) or data source (self-report versus objective data), suggesting that the finding is indeed robust and not an artefact of methodological flaws.

To control for potential publication bias, we additionally searched the grey literature for documents reporting on THN initiatives that are not published in the peer-reviewed journal domain. While this search was probably not exhaustive, the data reported in the grey literature are broadly consistent with the results of the studies included in our systematic review. For instance, in the Scottish National Naloxone Programme, in 2012 and 2013 the percentage of opioid-related deaths occurring within 4 weeks of prison release (5.5 and 4.7%) was almost half that of the pooled 2006–10 baseline indicator (9.8%), suggesting that distribution of naloxone kits on release may reduce the risk of fatal overdose among (former) prisoners with history of opioid use [48].

With regard to clinical implications, it needs to be emphasized that the vast majority of studies included in this review reported on heroin overdoses. Consequently, the generalizability of our findings to overdoses from long-acting opioids is unclear. Even when methadone patients were recruited specifically into a THN programme [33], more than 90% of witnessed (and reversed) overdoses were heroin-induced. The results of this review on the effectiveness of THN are thus limited to impact on heroin overdoses, and the effectiveness of the intervention for overdoses from long-acting opioids (e.g. methadone or many prescription opioids) needs to be explored in future research.

To conclude, application of the Bradford Hill criteria to the current evidence base from non-randomized studies finds that THN programmes have led to improved survival rates among programme participants and reduced heroin overdose mortality rates in the community (aim 1) and are accompanied by only a low rate of adverse events

(aim 2). In the absence of RCTs, we conclude that THN distribution to at-risk users should be introduced as standard of care for the community-based prevention of heroin overdose deaths.

Declaration of interests

R.M. has no interests to declare, except that R.M. and J.S. declare that King's College London (employer for both R.M. and J.S.) has registered intellectual property on a novel buccal naloxone formulation with which J.S. and R.M. are involved. J.S. declares that he is a researcher and clinician who has worked with a range of types of treatment and rehabilitation service-providers. He has also worked with a range of governmental and non-governmental organizations and with pharmaceutical companies to seek to identify new or improved treatments (including naloxone products), and from whom he and his employer (King's College London) have received research funding, honoraria, travel costs and/or consultancy payments. J.S. has also been named in a patent registration by a Pharma company as inventor of a further new naloxone formulation. For a fuller account of J.S.'s interests, see his personal web-page for King's College London at: http://www.kcl.ac.uk/ioppn/depts/addictions/people/hod.aspx. J.S. is supported by the National Institute for Health Research (NIHR) Biomedical Research Centre for Mental Health at South London and Maudsley NHS Foundation Trust and King's College London.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's web-site.

Appendix S1 Search protocol

ADDICTION
SSA SOCIETY FOR THE STUDY OF ADDICTION
FOR DEBATE
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Clinical provision of improvised nasal naloxone without experimental testing and without regulatory approval: imaginative shortcut or dangerous bypass of essential safety procedures?

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ABSTRACT

Context Take-home naloxone is increasingly provided to prevent heroin overdose deaths. Naloxone 0.4–2.0 mg is licensed for use by injection. Some clinicians supply improvised nasal naloxone kits (outside lisenced approval). Is this acceptable? **Aims** (1) To consider provision of improvised nasal naloxone in clinical practice and (2) to search for evidence for pharmacokinetics and effectiveness (versus injection). **Methods** (1) To document existing nasal naloxone schemes and published evidence of pharmacokinetics (systematic search of the CINAHL, Cochrane, EMBASE and MEDLINE databases and 18 records included in narrative synthesis). (2) To analyse ongoing studies investigating nasal naloxone (WHO International Clinical Trials Registry Platform and US NIH RePORT databases). **Findings** (1) Multiple studies report overdose reversals following administration of improvised intranasal naloxone. (2) Overdose reversal after nasal naloxone is frequent but may not always occur. (3) Until late 2015, the only commercially available naloxone concentrations were 0.4 mg/ml and 2 mg/2 ml. Nasal medications are typically 0.05–0.25 ml of fluid per nostril. The only published study of pharmacokinetics and bioavailability finds that nasal naloxone has poor bioavailability. **Questions for debate** (1) Why are pharmacokinetics and bioavailability data for nasal naloxone not available before incorporation into standard clinical practice? (2) Does nasal naloxone have the potential to become a reliable clinical formulation? (3) What pre-clinical and clinical studies should precede utilization of novel naloxone formulations as standard emergency medications? **Conclusions** The addictions treatment field has rushed prematurely into the use of improvised nasal naloxone kits. Evidence of adequate bioavailability and acceptable pharmacokinetic curves are vital preliminary steps, especially when effective approved formulations exist.

Keywords Death, emergency, heroin, naloxone, nasal, opioid, overdose, unlicensed.

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INTRODUCTION

Naloxone undoubtedly saves lives by reversing respiratory depression caused by heroin/opioid overdose. Analogous to the pre-provision of EpiPens for the peer-based emergency management of anaphylactic shock, practitioners in Chicago [1] and in a few locations in Europe [2] first began prescribing take-home naloxone for emergency use to heroin users (and family/peers) in the late 1990s in order to prevent overdose deaths from heroin or other opiates [3]. Take-home naloxone has been implemented by early adopters, but has become more mainstream only in the last 5 years, with the introduction of the first state-wide scheme in Massachusetts in 2008 [4] and first national schemes in Scotland and Wales in 2011 [5]. Take-home naloxone is now available in at least a dozen countries world-wide [6].

Systematic reviews conclude that pre-provision of naloxone is effective [7,8], and recent WHO Guidelines [9] recommend that anyone likely to witness an opioid overdose should have access to the antidote. Naloxone is approved for intravenous (i.v.), intramuscular (i.m.) or subcutaneous injection for treatment of heroin/opiate overdose [9].

Additionally, in the US, a new concentrated naloxone nasal spray was approved in Novemeber 2015 [10]. The recommended initial dose for the injection is 0.4 mg, which may then be increased to 2 mg, according to response, and may be repeated thereafter in extremis [9].

The notion of nasal naloxone is unquestionably attractive. It is quick to administer and reduces risk of needle-stick injury. However, until late 2015, naloxone for intranasal (i.n.) administration was not licensed anywhere in the world – neither for addiction or overdose treatment nor for any other indication. In November 2015, the situation changed with FDA approval (US only) of a naloxone nasal spray [10].

In this 'For Debate' paper, we consider we the widespread provision, by some services (parts of the US; parts of Australia; Norway; Denmark; parts of Scotland), of an improvised nasal naloxone kit (atomizer attached to prefilled syringe) for take-home naloxone [11,12]. This follows a practice used by some ambulance teams that administer naloxone off-licence as nasal spray [13]. However, the context of emergency care is fundamentally different from emergency care from a family member or peer with a nasal spray naloxone kit. In the ambulance context, the paramedic teams can give a naloxone injection when the nasal spray fails. However, no fallback treatment exists in the community setting for the family member or carer with only the nasal spray.

This 'For Debate' exploration neither condemns nor condones the pragmatic provision of improvised nasals spray by public health initiatives, particularly in communities where the distribution of injectable naloxone is politically not feasible. Rather, our aim is to stimulate discussion on the unlicensed use of new drug formulations in the addictions treatment field. Can we justify bypassing product testing and efficacy when licensed naloxone products already exist?

METHOD

The objectives for this examination are twofold: first, to report the practice of provision of nasal naloxone in clinical practice, and secondly to examine available published evidence of pharmacokinetics and effectiveness of naloxone by nasal administration (versus injection).

Search strategy

Replicating an earlier peer-reviewed search strategy [14], the CINAHL, Cochrane, EMBASE and MEDLINE databases were searched to identify relevant peer-reviewed English-language papers published between January 1946 and January (4th week) 2015 using the terms: 'naloxone.mp' or 'exp naloxone', 'narcan.mp.' or 'exp.Narcan' and 'exp administration, intranasal/or intranasal.mp' or 'nose.mp'. Two raters (B.T., R.M.) conducted the initial data searches, screened papers for eligibility and extracted data under the supervision of the senior investigator (J.S.). A total of 388 papers were retrieved and screened for original research (including case reports) reporting on pharmacokinetics, safety or effectiveness data of i.n. naloxone administration in healthy volunteers or patients with suspected opioid overdose. Eighteen records matched our search criteria [4,13,15–30] (see Table 1 and Fig. 1).

In addition, the WHO International Clinical Trials Registry Platform and US NIH RePORT database were searched for ongoing studies investigating nasal naloxone.

FINDINGS

Is i.n. naloxone already being prescribed in clinical practice?

Ambulance use

Nasal naloxone for treatment of opioid overdose was introduced as regular clinical practice (although without licence approval for this route) into ambulance services in parts of the United States (Denver, Colorado; Fresno, California; among others) in the 2000s [13,15,25], and in several National Health Service (NHS) Ambulance Service Trusts in the United Kingdom (including South Western, Great Western and East Midlands).

Take-home supply

Take-home naloxone as nasal spray only (i.e. without supplementary needle for i.m. injection) was first introduced in the United States in Boston, Massachusetts [4]. In 2013, 51 US organizations reported providing only i.n. naloxone [12]. In Europe, the Norwegian take-home naloxone scheme began providing only i.n. naloxone in 2014 [31]. At the time of writing, it is also proposed that the nasal spray will be the only form of naloxone provided in parts of Scotland (Inverness and surrounding regions Highland, Argyll and Buke) [11] and in France [32].

What is the evidence-base for i.n. naloxone?

No systematic review exists on nasal naloxone to date, but there is growing evidence of i.n. administration of naloxone reversing opioid overdose: at least 327 overdose reversals using nasal naloxone kits were reported in the Massachusetts-based take-home naloxone scheme [4,29,30]. In ambulance and hospital-based trials, the time from dose administration to clinical response often took longer for nasal administration compared to injectable routes [19,25,26]. However, for the comparison of i.n. and i.v. routes, this time difference disappeared when measuring the time from patient contact to clinical response due to the time saved for having to establish i.v. access [25]. Similarly, the time to clinical response was no different

Table 1 Summary of included studies.

Author (year)	*Study design*	*Setting*	*n*	*i.n. Dose*	*Dose comparator*	*Outcomes of naloxone administration*
Barton *et al.* [15]	Case series	Pre-hospital (EMS)	30 patients	2 mg (as 1 mg/ml)	2 mg i.v. if no immediate response	11 patients responded to naloxone challenge (i.n. or i.v.), of whom 10 (91%) responded to i.n. alone, with an average response time of 3.4 minutes
Barton *et al.* [13]	Case series	Pre-hospital (EMS)	95 patients	2 mg (as 1 mg/ml)	2 mg i.v. if no immediate response	52 patients responded to naloxone challenge (i.n. or i.v.), of whom 43 (83%) responded to i.n. alone, with an average response time of 4.2 minutes
Belz *et al.* [16]	Case series	Pre-hospital (EMS)	164 patients (108 i.v.; 29 i.v. + i.m.; 18 i.m.; 2 i.n.; 1 i.m. + i.n.; 6 NR)	Median 1 mg (0.2 mg-2 mg) across all routes of administration	i.v., i.m., i.v. + i.m., i.m. + i.n. (doses NR)	119 (73%) patients fully or partially responded to naloxone (for all routes of administration). 36 (22%) cases of death, 25 (15%) cases of agitation, 6 cases (4%) of emesis
Doe-Simkins *et al.* [4]	Pre–post comparison	Take-home naloxone	385 opioid users	2 mg (2 mg/2 ml)	None	Participants reported 74 successful OD reversals; no deaths
Dowling *et al.* [17]	Cross-over (open-label)	Laboratory (pharmacokinetics)	6 healthy volunteers	0.8 mg, 2 mg (as 0.4 mg/ml)	0.8 mg i.m., 0.8 mg i.v., 2 mg i.v.	The bioavailability was 36% for i.m. and 4% for i.n., both relative to i.v.
Green *et al.* [18]	Case report	Take-home naloxone	2 opioid users	2 mg (2 mg/2 ml)	None	Participants reported 2 successful OD reversals (self-administration); no deaths
Kelly *et al.* [19]	Randomized trial	Pre-hospital (EMS)	155 patients (71 i.m., 84 i.n.)	2 mg/5 ml	2 mg i.m.	The i.m. group had more rapid respiratory response than i.n. group (significant group difference in 'time to RR > 10/min' and 'spontaneous respiration within 8 min'). No group difference in GCS scores or need for rescue naloxone (13% i.m. versus 26% i.n.)
Kelly & Koutsogiannis [21]	Case report	Hospital (ED)	6 patients	0.8–2 mg	None	Across all patients, return of adequate spontaneous respiration occurred within a median 50 seconds (minimum 30 seconds, max. 2 minutes)
Kerr *et al.* [20]	Randomized trial	Pre-hospital (EMS)	172 patients (89 i.m., 83 i.n.)	2 mg (2 mg/ml)	2 mg i.m.	The rates of response within 10 minutes were similar: i.n. naloxone (60/83, 72.3%) compared with i.m. naloxone (69/89, 77.5%). No group difference in mean response time (i.n.: 8.0, i.m.: 7.9 minutes). Significant group difference in need for rescue naloxone: i.n. 18% versus i.m. 5%
Loimer *et al.* [22]	Controlled prospective trial (non-randomized)	Hospital (jail-based)	30 (22 opiate-dependent, 8 control)	1 mg (1 mg/0.4 ml)	None	After opioid challenge test of i.n. naloxone administration, opiate-dependent patients showed significantly higher ratings on withdrawal scale for up to 30 minutes (in comparison to controls)

(*Continues*)

Table 1. (Continued)

Author (year)	*Study design*	*Setting*	*n*	*i.n. Dose*	*Dose comparator*	*Outcomes of naloxone administration*
Loimer *et al.* [23]	Randomized trial	Hospital	17 patients (7 i.v. versus i.m.; 10 i.v. versus i.n.)	1 mg (1 mg/0.4 ml)	1 mg i.m. (1 mg i.v. as pre-treatment in both groups)	Both i.n. and i.m. groups showed significant withdrawal symptoms at 15 and 45 minutes. Only the i.n. group had significant withdrawal symptoms at 5 minutes, suggesting that onset of i.n. naloxone is faster than i.m.
Merlin *et al.* [24]	Retrospective chart review	Pre-hospital (EMS)	93 (38 i.n., 55 i.v.) (analysis of subsample of total 344 cases)	2 mg (1 mg per nostril)	i.v. naloxone titrated to effect (average 2 mg)	No group difference in RR or GCS pre-naloxone administration. Post-naloxone administration, both the median RR and GCS scores were significantly higher for the i.v. group than the i.n. group; 9 i.n. patients (23%) required rescue i.v. naloxone
Robertson *et al.* [25]	Retrospective chart review	Pre-hospital (EMS) and hospital (ED)	154 patients (50 i.n., 104 i.v.)	2 mg (1 mg per nostril)	1 mg i.v.	The time from dose administration to clinical response (pre-defined change in RR and GCS of 6 points) took significantly longer for i.n. route (12.9 versus 8.1 minutes). No group difference in overall time from patient contact to response. More i.n. patients received 2 doses of naloxone (34% versus 18%, $P = 0.05$), and 3 i.n. patients needed a rescue dose of i.v. or i.m. naloxone
Sabzghabaee *et al.* [26]	Randomized trial	Hospital (ED)	100 patients (50 i.n., 50 i.v.)	0.4 mg (0.4 mg/2 ml, i.e. 1 ml per nostril)	0.4 mg i.v.	Response to naloxone was significantly slower in i.n. group. Patients in i.n. naloxone had higher GCS scores but lower heart rate than i.v. group. No group difference in blood pressure, RR, arterial O_2 saturation or length of hospital stay
Walley *et al.* [29]	Interrupted time–series analysis	Take-home naloxone	2912 opioid users	2 mg (2 mg/2 ml)	Communities without take-home naloxone	Participants reported 327 successful OD reversals; no deaths. Across the 19 participating communities, OD mortality rates were reduced in communities with THN, compared to those without
Walley *et al.* [30]	Pre–post comparison	Take-home naloxone	1553 methadone clients	2 mg (2 mg/2 ml)	None	Methadone clients reported 92 successful OD reversals; no deaths
Weber *et al.* [27]	Retrospective chart review	Pre-hospital (EMS)	105 patients	2 mg (2 mg/3 ml)	None	Of all 105 cases, 23 (22%) had complete response, 62 (59%) partial response, and 20 (19%) no response, as indicated by GCS score and RR. Eleven cases (10%) received rescue naloxone (6 i.v., 5 i.m.). No adverse events or deaths occurred
Zuckerman *et al.* [28]	Case report	Pre-hospital (EMS) and hospital (ED)	1 patient	2 mg (1 mg per nostril)	None	After non-response to i.n. dose, patient was administered 3 i.v. rescue doses (1 mg + 0.4 mg + 0.4 mg) by EMS and ED staff

ED = emergency department; EMS = emergency medical services; GCS = Glasgow Coma Scale; i.m. = intramuscular; i.n. = intranasal; i.v. = intravenous; NR = not reported; RR = respiration rate; OD = overdose; THN = take-home naloxone.

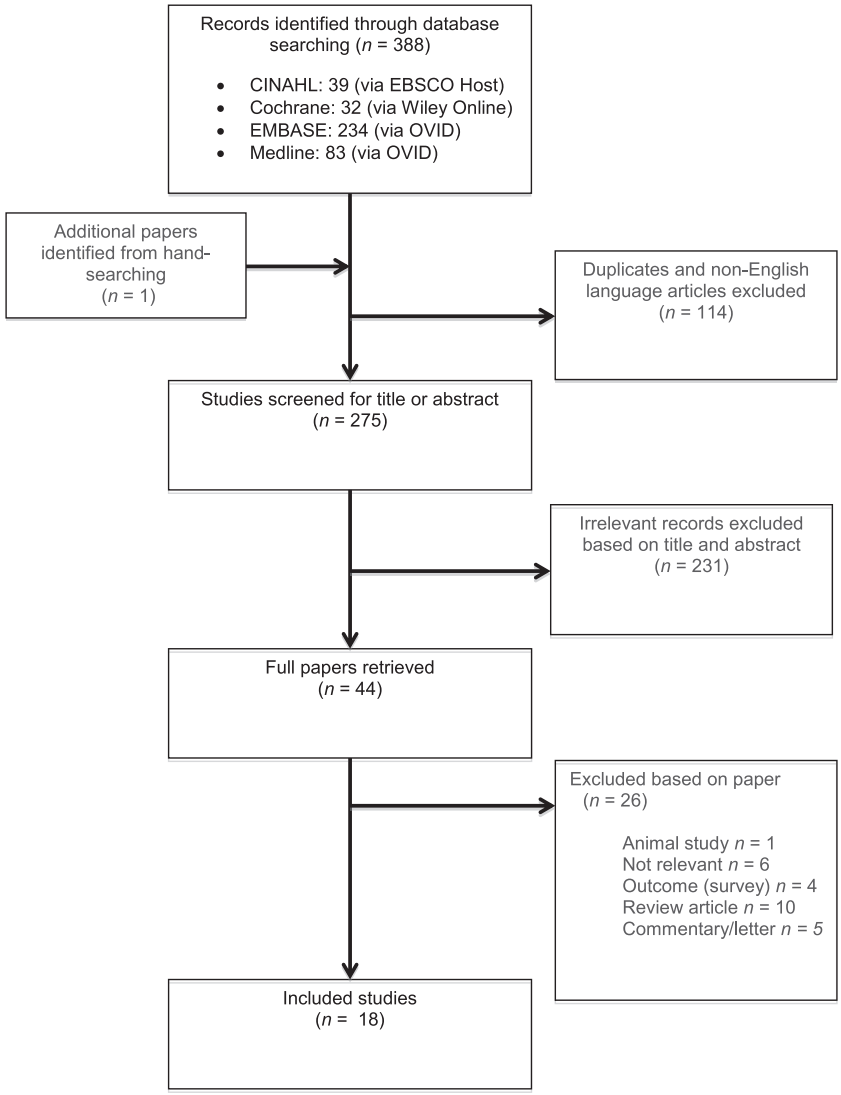

Figure 1 Flowchart of study selection

from i.m. administration when a more concentrated nasal spray formulation (2 mg/ml) was used [20].

However, with concerns as summarized below, there remains a lack of information about how adequately and reliably naloxone is absorbed intranasally.

Lack of simple pharmacokinetics

Progress with basic pharmacokinetic study of i.n. naloxone has been slow. The only published pharmacokinetic study [17] reported extremely poor bioavailability (4%) for nasal naloxone (although the authors acknowledged that the dilute solution probably resulted in post-nasal loss or nasal leakage). Despite reports of replication studies (e.g. by pharmaceutical companies), no new pharmacokinetics data have yet been published in the peer-reviewed domain.

Non-response rate

The results from ambulance-based studies in Australia [18,19] and the United States [12,14,23,26] indicate that not all opioid overdose victims respond to nasal naloxone, with some needing a rescue dose of i.m. or i.v. naloxone (see also Table 1). An ambulance-based randomized trial in Australia compared i.n. to i.m. naloxone: in a moderate proportion of instances the i.n. initial dose was not sufficient. Furthermore, it was not equal—the i.n. group was twice as likely to require rescue naloxone [26% i.n. group versus 13% i.m. group; $P = 0.056$; odds ratio (OR) = 2.4; 95% confidence interval (CI) = 1.0–5.7) [18]. In a replication trial with a more concentrated nasal spray formulation (2 mg/ml), 18% of the i.n. group still needed rescue naloxone, which was significantly higher than the i.m. group (5%) [19]. This rate is broadly consistent with

16% of i.n. non-responders in a Denver-based observational trial [13]. Other studies have reported non-response rates between 9 and 23% [15,24,27].

Ongoing research

Clinical trials are currently being conducted in the ambulance setting in Cincinnati, USA, and in a supervised injecting clinic in Sydney, Australia.

Pharmacokinetic exploration of i.n. formulations is finally under way by two groups in the United States and one in Norway: however, no results are yet published.

Other potential non-injectable routes warrant consideration. Rectal suppositories would almost certainly be effective, but probably with poor acceptability to family and peers. The oral cavity is the obvious alternative: however, sublingual naloxone had poor bioavailability with marked intersubject variability in an opioid-using sample [33]. In contrast, the buccal route was found to have high naloxone bioavailability in rodents [34], and has been successful with other emergency medications; for example, buccal midazolam is now licensed for family use for interim management of seizures or status epilepticus [35]. We are currently examining the pharmacokinetics of buccal naloxone (EudraCT: 2014–001 802–16).

Reasons for caution

The concerns raised in this paper relate to the use of improvised nasal sprays based on dilute solutions of naloxone developed for injection and not examined for suitability or efficacy as nasal spray. A recent step-change, in November 2015, was the licensing by FDA in the US of a naloxone nasal spray [10] which evidently met their pre-specified criteria of comparability of effect to injectable naloxone. Another application for a naloxone nasal spray was unsuccessful because it was found not to be absorbed sufficiently rapidly [36]. In our opinion, there remain the following crucial considerations:

First, non-response rates of between 9 and 26% have been reported for nasal naloxone [13,15,19,20,24,27]. As noted in the Introduction section, there is an inherent safety in the use of nasal naloxone in the ambulance or hospital context, where a naloxone injection can be administered in the event that the initial nasal naloxone does not reverse overdose. However, in the recently introduced take-home naloxone schemes that provide naloxone only for i.n. use [4], the absence of a back-up injection is a crucial difference. In this situation the failure of effect of i.n. naloxone, for whatever reason, can delay the time to naloxone injection until an ambulance arrives. In the emergency management of opioid-induced respiratory depression, time is of the essence.

Secondly, there is still uncertainty about dose adequacy and comparability of nasal naloxone. For the improvised nasal spray, the only commercially available injectable formulations have concentrations of either 0.4mg/ml or 1mg/ml (adult formulations). Drug administration via nasal spray typically involves giving 0.1 ml per nostril, with 0.25 ml considered the maximum, as any greater volume is probably lost post-nasally (and then swallowed and consequently inactivated) or by nasal drip (and thereby lost) [17].

Some consideration of the practical administration of the naloxone as nasal spray is warranted. The most concentrated formulation available of naloxone is 2 mg/2 ml. If this concentration of naloxone is administered at 0.25 ml per nostril, then, even if we discount the reported nasal bioavailability of 4% [17] and assume optimistically that 40% of naloxone is absorbed, the effective i.n. dose would be only 0.2 mg, i.e. equivalent to only half the lower recommended injectable dose. The remainder would be lost as nasal drip or as post-nasal drip (and inactivation).

Given the small dose that is probably absorbed, reported benefit from improvised nasal devices (see Table 1) is puzzling: this should prompt challenge to assumptions about naloxone dose–response. Dose-ranging studies with dependent volunteers could explore this sensitively.

Thirdly, at a practical level, uncertainties about the effectiveness of a nasal spray include: the need for a spray device to function in horizontal position, the impact of compromised nasal mucosa (e.g. chronic ulceration from drug snorting [37]) and the risk of nasal obstruction from opioid-induced vomit. Any factors which reduce or delay the absorption of naloxone may lessen the overdose victim's chance of survival.

QUESTIONS FOR DEBATE

What data should be available on nasal naloxone formulations?

If we are considering introduction of a novel non-injectable formulation of naloxone, then we have a responsibility to be confident that the non-injectable form is absorbed equivalently or to a sufficient extent so as to produce the life-saving reversal of opioid effect (for which emergency reason it is being given). It is not obvious that nasal administration would be equivalent in healthy volunteers, and even less clear when administered in an emergency situation to an overdose victim whose drug use may include damage to nasal mucosa and structure and also whose crisis overdose may have resulted in vomitus or secretions in the nasal cavity. These challenges need to be examined and addressed. Pharmacokinetics and study of bioavailability need to be undertaken and published showing acceptable availability and reliability before incorporation into standard clinical practice: until such data are presented publicly, clinicians should not consider a hypothetical new route of administration as necessarily reliable.

Can we list the probable necessary specifications for an acceptable non-injectable formulation of naloxone?

We can already list some of the profile of what we would expect an acceptable nasal naloxone formulation to look like. In view of the emergency context of the resuscitation and the probably unconscious state of the overdose victim, the nasal device would need to be functional in all orientations (i.e. not just when held vertically, as with many nasal sprays). If 0.25 ml of fluid can be absorbed per nostril, and if we put to one side the Dowling finding of 4% bioavailability and assume a more optimistic 40% bioavailability for nasal naloxone, then a more concentrated solution is required—perhaps between 4 mg/ml up to 20 mg/ml. Fortunately, naloxone is highly soluble, so this should not be a problem, provided that there are no adverse local effects. It also needs to be established that the speed of onset of effect is sufficient. It needs to be more than simply evidence of adequate absorption with a good area under the curve (AUC) because, for this emergency situation, it is essential that the absorption occurs rapidly. We suggest a rapid onset of action with detectable effect within 5 minutes and good effect within 10 minutes. Measures of T_{max} (i.e. the time at which the maximum blood serum concentration of naloxone is observed) may not capture the shape of onset of effect, and so we suggest also measuring $T_{50\%}$ (by which we mean the time taken to achieve blood levels of 50% of those subsequently recorded as C_{max}). (There may also be value in measuring W_{max} to examine length of time before blood level drops below 50% of the value achieved as C_{max}).

Clinical experimental studies should be conducted with opiate-dependent volunteer subjects as well as with healthy volunteer subjects

A distinct advantage of experimental study of non-injectable naloxone formulations with dependent volunteers is that the rate of absorption of naloxone and the onset of brain effect can be detected very sensitively (alongside blood levels), as the naloxone will be detectable immediately through onset of opiate withdrawal symptoms. While this may be distressing to the dependent volunteer subjects (and while the ethics and the information and discussion will need careful discussion and exploration), this is the most powerful experimental approach to testing such proposed alternative naloxone products. A current example of a clinical trial in dependent volunteers is the Australian randomized, double-blind clinical trial comparing i.n. versus i.m. naloxone in clients of the Sydney Medically Supervised Injecting Centre (currently in progress). Furthermore, if the relative bioavailability of a novel nasal formulation is high, there may be implications for the safety profile [38], which would not be detected in healthy volunteers.

Implications of the prior existence of an approved licensed injectable naloxone

Some consideration needs to be given to why a clinician would prescribe naloxone for use by an unlicensed route, when a highly effective, licensed injection is already in their armamentarium. Perhaps the nasal spray relieves ayperson anxiety about giving an i.m. injection. However, families of patients with other disorders overcome this fear successfully (e.g. EpiPen, glucagon). Training in technique is necessary, but this can be conducted efficiently and bolsters the confidence of family and peers to intervene [39]. In jurisdictions where laypeople (including family members) are prohibited from administering emergency medications by injection, there should be urgent challenge of this obstacle. We posit that, wherever possible, clinicians should prescribe medications for use by the approved route of proven effectiveness.

Medico-legal risks considerations

It also needs to be borne in mind that medico-professional and medico-legal risks may arise when naloxone is prescribed for use by unlicensed route, especially when licensed naloxone products are applicable. If death were to occur following nasal administration, what reason would justify having provided naloxone for use by an unlicensed route?

Cost considerations

The pricing of novel naloxone products is currently uncertain and possibly variable. Affordability relative to existing injectable products will be crucial, particularly for the proposed population-wide provision of emergency naloxone, as articulated by the World Health Organization [9].

CONCLUSION

There are good reasons to want a non-injectable naloxone preparation for treating opioid overdose to work. However, wishing for a product is not the same as demonstrating efficacy and effectiveness. The benchmark for any non-injectable naloxone product, if considered for wider community use, should be that it is, in general terms, at least as effective and reliable as the licensed injection.

Description of use of improvised nasal formulations should not be accepted as evidence of effectiveness. Actual data need to be published and need to report not only on whether it is effective in some subjects, but also whether it is effective in all subjects. If no injectable comparator existed, then a new overdose resuscitation medication that was effective for many subjects would be valued, even if it was not effective for all subjects. However, as an established licensed injectable naloxone with proven efficacy and good

safety profile already exists, the expectations for a potential new naloxone formulations are at a higher bar.

In the US, in November 2015, the FDA granted approval to a naloxone nasal spray [10] which we understand to be a concentrated nasal spray delivering a 4mg naloxone dose in a 0.1ml volume through what appears to be an Aptar single-dose liquid nasal spray device [40]. This approval was issued while this 'For Debate' was in press, but we have had opportunity to add brief consideration. This FDA approval only applies to US territory, and is as a prescription-only medicine, although special local arrangements allow pharmacists to sell naloxone without a prescription in at least 15 US states. A competitor nasal spray product was denied FDA approval [36]. This prompts us to offer the following additional observations, for debate. Firstly it is a welcome development to see the appearance of a tested and approved naloxone nasal spray. At present this is only available in the US although we anticipate it will be submitted for consideration in other countries in the near future. We look forward to seeing more PK information on the new approved nasal spray. Secondly the denial of approval for the competitor nasal spray was because of insufficiently rapid absorption (relative to the injectable naloxone reference). This accords with the concerns described above. We need proper examination and scrutiny of proposed use of medications outside their tested and licensed routes of administration. For example, the relative bioavailability of the improvised nasal spray (which we consider above) was found to be only approximately 10% compared to relative bioavailability of 30-40% for the new concentrated nasal spray. Thirdly clinicians need this information on relative bioavailability and extent of inter-individual variability so that they can make correct clinical decisions on dose adjustment for the new nasal spray (relative to the established injectable formulations for which dose guidance has been developed).

To conclude, outside clinical trial contexts, clinicians should prescribe take-home naloxone only as one of its licensed formulations, since it remains uncertain how adequately and reliably the improvised nasal spray is absorbed. Or, if clinicians choose to prescribe the improvised naloxone nasal spray off-licence, then they should include a needle in the naloxone kit to allow for a back-up injection if the nasal spray is insufficient.

Declaration of interests

J.S. is a researcher and clinician and has had, and continues to have, clinical responsibilities and has worked with a range of types of treatment and rehabilitation service-providers. He has contributed to the work of various governmental and non-governmental organizations and has received project grant support and/or honoraria and/or consultancy payments from Department of Health, NTA (National Treatment Agency), PHE (Public Health England), Home Office, NICE (National Institute for Health and Clinical Excellence) and EMCDDA (European Monitoring Centre for Drugs and Drug Addiction), as well as research grants from (last 3 years) NIHR (National Institute on Health Research), MRC (Medical Research Council) and Pilgrim Trust. He has also worked with pharmaceutical companies to seek to identify new or improved treatments including naloxone products (including, last 3 years, Martindale, Reckitt-Benkiser/Indivior, Lundbeck, MundiPharma, Rusan/iGen), from whom he and his employer (King's College London) have received honoraria, travel costs and/or consultancy payments. His employer (King's College London) has registered intellectual property on a novel buccal naloxone (with which J.S. and R.M. are involved), and J.S. has also been named in a patent registration by a Pharma company (declared above) as inventor of a potential concentrated naloxone nasal formulation. A fuller account of his interests is at http://www.kcl.ac.uk/ioppn/depts/addictions/people/hod.aspx. R.M.'s employer (King's College London) has registered intellectual property on a novel buccal naloxone. R.M. has no other interests to declare. B.T. and E.D. have no interests to declare.

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Review

Naloxone without the needle – systematic review of candidate routes for non-injectable naloxone for opioid overdose reversal

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ABSTRACT

Introduction: Deaths from opioid overdose can be prevented through administration of the antagonist naloxone, which has been licensed for injection since the 1970s. To support wider availability of naloxone in community settings, novel non-injectable naloxone formulations are being developed, suitable for emergency use by non-medical personnel.
Objectives: 1) Identify candidate routes of injection-free naloxone administration potentially suitable for emergency overdose reversal; 2) consider pathways for developing and evaluating novel naloxone formulations.
Methods: A three-stage analysis of candidate routes of administration was conducted: 1) assessment of all 112 routes of administration identified by FDA against exclusion criteria. 2) Scrutiny of empirical data for identified candidate routes, searching PubMed and WHO International Clinical Trials Registry Platform using search terms "naloxone AND [route of administration]". 3) Examination of routes for feasibility and against the inclusion criteria.
Results: Only three routes of administration met inclusion criteria: nasal, sublingual and buccal. Products are currently in development and being studied. Pharmacokinetic data exist only for nasal naloxone, for which product development is more advanced, and one concentrated nasal spray was granted licence in the US in 2015. However, buccal naloxone may also be viable and may have different characteristics.
Conclusion: After 40 years of injection-based naloxone treatment, non-injectable routes are finally being developed. Nasal naloxone has recently been approved and will soon be field-tested, buccal naloxone holds promise, and it is unclear what sublingual naloxone will contribute. Development and approval of reliable non-injectable formulations will facilitate wider naloxone provision across the community internationally.

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1. Introduction

1.1. An excess of deaths

Heroin/opioid overdose deaths represent a major international public health concern (UNODC/WHO, 2013). Even in countries with low prevalence of opioid use relative to consumption of other illicit drugs, opioids contribute disproportionately to overdose fatalities (Degenhardt et al., 2011; WHO, 2014). In the United States (US), there has been a greater than fourfold increase in overdose deaths from prescription opioids since 1999, accounting for 16,651 deaths in 2010 alone (CDC, 2012; Volkow et al., 2014), as well as a simultaneous rise in heroin overdose deaths from 2007 onwards (Calcaterra et al., 2013). In the United Kingdom (UK), a 64% rise in heroin/morphine deaths was recorded for England and Wales between 2012 and 2014 (ONS, 2015).

1.2. Wider provision of naloxone

In response, there are increasing calls for wider access to the opioid antagonist naloxone (ACMD, 2012; UNODC/WHO, 2013). The World Health Organization (WHO) launched new guidelines on the prevention of opioid overdose deaths in 2014, recommending that "people likely to witness an opioid overdose should have accesss to naloxone" (p. x) (WHO, 2014).

In the US, the National Institute on Drug Abuse (NIDA) made funding available for the development of novel injection-free naloxone products (Volkow et al., 2014) and, in November 2015, the US Food and Drug Administration (FDA) gave approval to a new nasal spray of concentrated naloxone solution (FDA, 2015), thereby giving the first regulatory product approval worldwide for a non-injectable naloxone product.

1.3. The promise of non-injectable naloxone

The notion of non-injectable formulations of naloxone is attractive: naloxone without needles would have many advantages. Firstly, medications which need to be injected are intimidating for lay persons to use in non-medical settings (Beletsky et al., 2012). Secondly, with use of naloxone by injection, there is the risk of needle-stick injury and contraction of blood-borne diseases (e.g., hepatitis C, HIV), which are highly prevalent among this patient group. Thirdly, non-injectable naloxone could more easily be provided to a much wider intervention workforce (e.g., hostel staff, outreach workers, police, etc.).

New methods of delivery for naloxone need to be suitable for emergency use by non-medical personnel in community-based settings. Furthermore, formulations should be developed with longer shelf-life, especially in view of the pre-placement of these naloxone products to community and families and other non-hospital settings. Naloxone also needs to be absorbed rapidly, given the emergency situation, in quantity sufficient to effect quick reversal of opioid-induced respiratory depression.

The reference for any candidate non-injectable routes is injectable naloxone, administered by the licensed intramuscular (IM), intravenous (IV), and subcutaneous (S/C) routes (WHO, 2014). When administered by the IM or S/C routes, naloxone typically reverses opioid action within 3–7 min; whereas the effect from IV administration has an onset typically within 2 min (UNODC/WHO, 2013). With long-standing approval for, and experience with, naloxone in injectable form, this sets the standard against which possible non-injectable formulations need to be measured (Hertz, 2012). In this review, we examine the options for non-injectable naloxone with potential application for wider community-based opioid overdose reversal.

2. Material and methods

A three-stage approach has been taken (see Fig. 1). The first stage was an examination of all 112 routes of drug administration listed by the US Food and Drug Administration (FDA, 1992) updated 2014). For each of the 112 possible routes of administration, we considered the potential applicability as a viable non-injectable route for emergency naloxone delivery by non-medical personnel (see Supplementary Material). We thus identified routes as unsuitable according to five exclusion criteria:

i) If the drug administration is by injection (or similar invasive procedure);
ii) If the route is only relevant to medical procedures or requires medical training;
iii) If the route is not publicly acceptable for administration by non-medical bystanders (e.g., rectal or vaginal administration);
iv) If the route does not produce adequate systemic drug concentrations;
v) If the route does not produce sufficiently rapid drug absorption relative to parenteral administration (Hertz, 2012).

The second stage was to systematically search PubMed and the WHO International Clinical Trials Registry Platform for the potential candidate routes of administration that had emerged from the first stage. The search term "naloxone AND [route of administration]" (e.g., "naloxone AND (nose OR nasal OR intranasal)") was used for each route across the electronic databases (see Supplementary Material for search protocol). R.M. conducted the search and assessed retrieved studies for eligibility under supervision of J.S.

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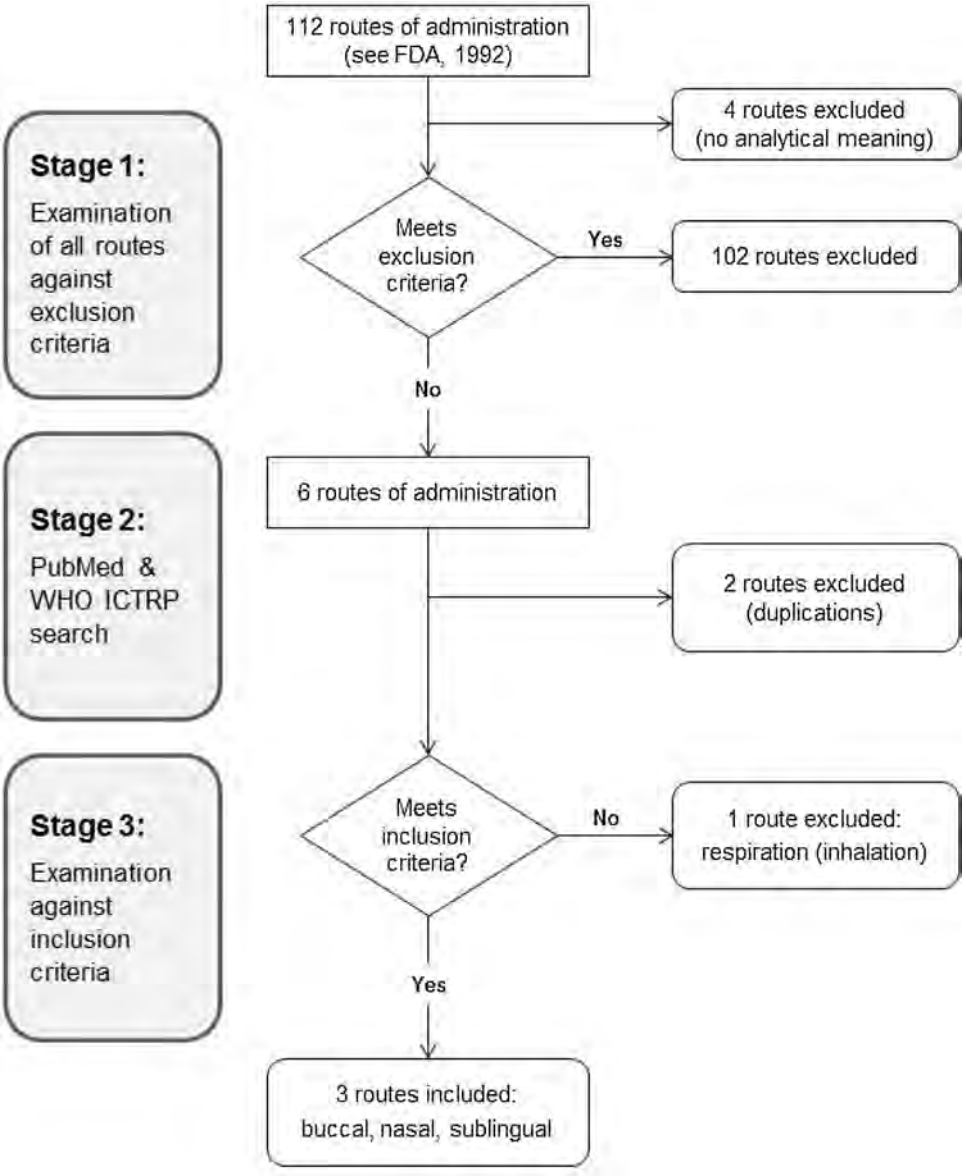

Fig. 1. Selection process of candidate routes of administration.

Relevant original research studies that were published in English language and reported on the outcomes of in vivo naloxone administration (e.g., overdose reversals, pharmacokinetics/-dynamics data) in humans or animals were included in our analysis (see Fig. 2 for PRISMA diagram).

The third stage, for remaining potential non-injectable routes of administration, comprised a more rigorous examination of the evidence against the inclusion criteria (see also Table 1):

i) The route is suitable for overdose emergency situation.
ii) The route does not bear major risk of compromise from overdose complication.

For the first and third stage, R.M. and J.S. used the specified exclusion and inclusion criteria to independently screen all relevant routes of administration for potential inclusion. When the reviewers reached different decisions, B.F. acted as the final arbitrator for inclusion or exclusion of a route.

3. Results

3.1. Shortlisting potential non-injectable routes from analysis of all routes of administration

From examination of all 112 listed routes of administration (FDA, 1992), four were excluded on the basis that they held no analytic relevance ('unassigned', 'unknown', 'other' and 'not applicable'). From the remaining 108 categories, a further 102 were excluded according to the criteria listed in 'Method' (see determination in Supplementary Material). For instance, enteral delivery (through the gastro-intestinal mucosa) was excluded because of insufficient systemic absorption, since naloxone is poorly bioavailable if swallowed due to high first-pass metabolism (Fishman et al., 1973). After this process, six non-injectable candidate routes remained to be considered further (see Table 1).

We then removed two of these six routes (see bottom of Table 1) on the basis that they were overarching categories of routes already being considered. Thus 'oropharyngeal' was removed as substantially overlapping with 'buccal' and 'sublingual', and 'transmucosal'

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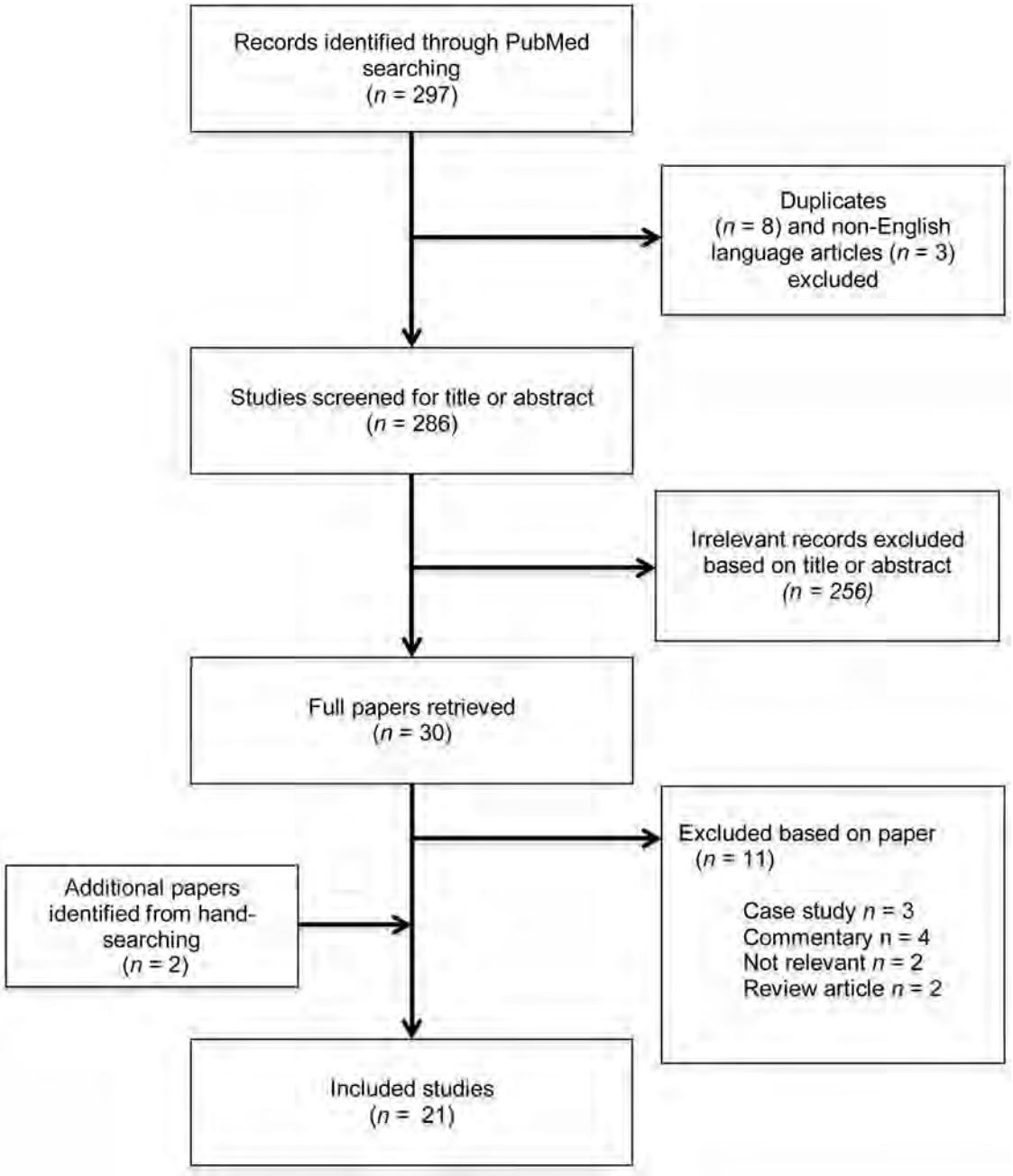

Fig. 2. PRISMA flow diagram of study selection process.

was removed and considered under the specific mucosa ('buccal', 'intranasal', 'sublingual'). With regard to the wider range of possible transmucosal routes, rectal delivery, which has replaced administration by injection for several emergency medications in paediactric care (Lyon and McIntosh, 1985; NICE, 2009), was specifically not included for further consideration since it is unlikely to be acceptable to family and peers for community-based naloxone emergency administration to overdose victims.

3.2. Fuller examination of the four shortlisted potential non-injectable routes

We next examined more fully these four potential routes (buccal, nasal, sublingual, respiratory/inhalation) based on the literature retrieved from the electronic databases. According to the WHO International Clinical Trials Registry Platform, nasal naloxone is currently being investigated in clinical trials by the Norwegian University of Science and Technology (NCT02307721, NCT01939444), in the US by the University of Cincinnati (NCT01912573) and Lightlake Sinclair Ltd. (NCT01567670), in Jordan by Mitovie Pharma Ltd. (NCT01622504), and in Australia at the Sydney Medically Supervised Injecting Centre (ACTRN12611000852954). Buccal naloxone is currently being studied at King's College London in the UK (EudraCT 20140001802-16 & 2016-000582-23; see below). No database entries were found for study of naloxone via the sublingual or respiratory/inhalation routes.

We then consider each of these in turn:

3.2.1. Respiratory (inhalation). We excluded the 'Respiratory (Inhalation)' route as not being suitable for further consideration because the victim might no longer be breathing (or breathing only very shallowly). Further, current portable devices for drug delivery

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Table 1
Third stage of selection of potential routes of administration: inclusion criteria.

Name	Definition	FDA Code	Inclusion criteria	
			Suitable for overdose crisis situation	No risk of compromise from overdose complication
Buccal	Administration directed toward the cheek, generally from within the mouth	030	X	X
Nasal	Administration to the nose; administered by way of the nose	014	X	Possible impairment due to O/D vomit or secretions
Sublingual	Administration beneath the tongue	024	X	Possible impairment due to O/D vomit or secretions or due to closed mouth
Respiratory (inhalation)	Administration within the respiratory tract by inhaling orally or nasally for local or systemic effect	136	Not viable as O/D victim not breathing or only shallowly	X
With the following routes subsumed into the above four routes:				
Oropharyngeal	Administration directly to the mouth and pharynx	410	Absorption likely to be too slow	Possible impairment due to O/D vomit or secretions
Transmucosal	Administration across the mucosa	122		- As for buccal -

to the lungs could not be used reliably in an emergency situation by non-medical personnel (spray or aerosolized naloxone is better considered under the 'nasal' category).

3.2.2. Sublingual. For the sublingual route, PubMed identified one pharmacodynamics study in opioid-dependent volunteers, where sublingual naloxone precipitated withdrawal symptoms in 5 out of 9 participants (Preston et al., 1990). Apart from separate work on buprenorphine/naloxone combination, no further investigative work for sublingual was identified.

3.2.3. Nasal. PubMed search yielded 18 studies reporting in vivo administration of intranasal naloxone. Preclinical data from rodent studies showed complete absorption of nasal naloxone (bioavailability relative to IV: F% = 101%; Hussain et al., 1984). In first in-human trials, nasal naloxone was found to elicit withdrawal symptoms in opioid-dependent volunteers (Loimer et al., 1992, 1994). Since the early 2000s, nasal naloxone has been used off-label by ambulance personnel (Barton et al., 2005, 2002; Belz et al., 2006; Kelly et al., 2005; Kerr et al., 2009; Merlin et al., 2010; Robertson et al., 2009; Weber et al., 2012) and in the emergency department (Sabzghabaee et al., 2014). More recently, improvised nasal kits (consisting of a pre-filled naloxone syringe and an atomizer which fits onto the syringe to generate a nasal spray) have been provided to opioid users, peers, and families in take-home naloxone trials (Doe-Simkins et al., 2009; Dwyer et al., 2015; Walley et al., 2013a, 2013b), and succesful overdose reversals using improvised nasal kits have also been reported for police first responders (Rando et al., 2015). However, the only published pharmacokinetics study in humans found intranasal naloxone (2 mg/5 mL) had a relative bioavailability of only 4% (Dowling et al., 2008).

3.2.4. Buccal. PubMed search identified two preclinical studies on buccal naloxone. In rodents, buccal naloxone administration led to high bioavailability (F% = 69–71%) and a T_{max} of 24 min (Hussain et al., 1987, 1988), whereas in dogs, despite buccal T_{max} at 18 min, bioavailability was low (16%) (Hussain et al., 1988).

Consequently, only three routes of administration are carried forward for full consideration as candidate routes of administration for emergency naloxone by non-medical personnel: nasal, sublingual and buccal. We now compare all three routes more fully against the FDA-identified reference route (injectable naloxone) (Hertz, 2012).

3.3. Testing requirements for potential new routes of administration (nasal, sublingual and buccal)

For all three identified candidates non-injectable routes (nasal, sublingual and buccal), investigators and manufacturers need to consider the FDA guidance on development of novel naloxone formulations for outpatient use (Hertz, 2012). The FDA proposed this strategy mindful of the good safety profile of naloxone: while naloxone blocks opiate receptors, it has no pharmacological effect in individuals who are not opiate-dependent and do not have any opioids in their system. Moreover, as it has no potential of abuse due to lack of euphoriant effect (Brunton et al., 2010), the pharmacokinetics of novel naloxone formulations can be safely tested in healthy volunteers. According to the FDA guidance (Hertz, 2012), pharmacokinetic studies will need to "[e]valuate the relative bioavailability of at least two different doses compared to parenteral injection of naloxone (IM, IV or SC). [Studies should] [c]ompare a parenteral dose of naloxone of at least 0.4 mg to dose(s) of the new product that would be expected to result in similar or greater drug exposure. Target plasma naloxone levels [should be] detectable in all subjects for a meaningful duration comparable to approved product."

The FDA guidance (Hertz, 2012) outlines the following key questions concerning the bioavailability and usability of a new product:

1) "If the relative bioavailability is low, will there be adequate efficacy? If the relative bioavailability is high, are there implications for the safety profile?"
2) "Can the product be used by the intended population, i.e. [is] administration by someone other than the patient [possible]?"

For all potential non-injectable naloxone products, it will be important to focus on absorption within the first 20–30 min. For emergency overdose applications, any novel naloxone product will need to be absorbed rapidly into the bloodstream and thence across the blood-brain barrier. This is plausible for the nasal, buccal and sublingual routes, since they all involve absorption across a mucous membrane outside the gastro-intestinal tract. They drain to the peripheral circulation rather than the hepatic portal vein, thus avoiding the hepatic portal system and first-pass metabolism in the liver.

The nasal route is characterized by high blood perfusion of the nasal mucosa which facilitates transmucosal absorption, and drainage mainly occurs into the facial veins (Dale et al., 2006; Standring, 2015). The buccal route (from the oral vestibular cavity) and the sublingual route both drain into the internal jugular

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vein via the facial veins, and thence rapidly to the brain (Standring, 2015).

For nasal administration, Ehrick et al. (2013) identify three mechanisms as significant (inertial impaction, gravitational sedimentation, and Brownian diffusion) of which they identify inertial impaction as the most important mechanism, with absorption understood to take place primarily in the posterior/respiratory zone of the nasal cavity (Ehrick et al., 2013). Additionally, a nose-to-brain (N2B) connection has been hypothesized. It is mooted that drugs could be transported directly into the cerebrospinal fluid via the olfactory and trigeminal nerves (Djupesland et al., 2014) through the olfactory epithelium (on the roof of the nasal cavity) projecting directly into the olfactory bulb. However, human evidence of direct drug transport from the nose to the cerebrospinal fluid is currently still lacking (Djupesland et al., 2014; Merkus et al., 2003).

In addition to these anatomical and pharmacological factors, we need to consider the context of emergency overdose reversal (e.g., devices need to be portable, accessible, easy to use and also operational on an unconscious supine overdose victim) as well as the physical health of the target population, including potential damage to, or obstruction of, the relevant mucosa.

3.3.1. Intranasal. Clinical reports describe use of improvised nasal naloxone kits which indicate life-saving benefit in many situations (see Results 3.2). However, for non-concentrate nasal kits, there remains uncertainty with regard to the formulation's bioavailability and reliability of clinical effectiveness (Strang et al., 2016). For example, Dowling et al. (2008) found that non-concentrate nasal naloxone spray (2 mg/5 mL) had a bioavailability of only 4%, although the authors themselves acknowledged that the poor absorption was likely due to the insufficiently concentrated formulation.

In two ambulance-based clinical trials, intranasal naloxone had a substantial non-response rate: among opioid overdose victims, 26% (using 2 mg/5 mL nasal formulation; Kelly et al., 2005) and 18% (using 2 mg/mL nasal formulation; Kerr et al., 2009) required a second rescue dose of naloxone (the second dose given IM).

For a purpose-developed nasal naloxone spray, a more concentrated formulation of naloxone should be used, e.g., at least 5–10× current concentrations, a) to overcome the drug loss associated with administration of excessive volumes to the nasal cavity and b) to administer naloxone across the recommended dose range (i.e. bioequivalent to 0.4–2 mg IV or IM).

A significant positive development in this regard is the recent FDA approval of a new nasal spray formulation of a concentrated naloxone solution (US territory only) (FDA, 2015). Pharmacokinetics data (including dose-equivalence and constancy) on concentrated naloxone nasal spray will hopefully become available and it will be important to field-test the new product to assess the potential significance of practical obstacles, e.g., inter-individual variability, impact of airway blockage or apnea, impact of vomitus in the nasal passages or mouth, impact of nasal mucosal damage from drug abuse. This is necessary because drug users may have damaged nasal mucosa – for example, ulceration, scarring and loss of tissue from repeated cocaine use (Peyrière et al., 2013). Absorption may consequently vary substantially between individuals, making it difficult to achieve systemic drug levels rapidly and reliably. There is also the possibility of interference with nasal absorption from vomiting associated with the overdose, thereby rendering the nasal cavity compromised.

3.3.1. Sublingual. An FDA product application was submitted in 2015 for a sublingual naloxone spray (FDAnews, 2015). If the naloxone were to be absorbed rapidly and efficiently, then this could be viable. However, there are several concerns regarding the suitability of the sublingual route for the emergency administration of naloxone. Access to the mucosa under the tongue may be obstructed if the mouth of the overdose victim is closed and/or if vomiting has occurred. A sublingual spray would be difficult to administer, as liquid may be lost to swallowing. Sublingual tablets are typically small and would be hard to position. Furthermore, significant inter-subject variability of sublingual naloxone delivery and effect was observed in a pharmacodynamics study in opioid users (Preston et al., 1990).

3.3.2. Buccal. Despite lack of human in vivo data for buccal naloxone, we see merit in exploration of the option of a solid-form rapid-dispersal buccal tablet formulation. Working between the Addictions Department and the Institute of Pharmaceutical Science at King's College London, we have developed a working prototype lyophilised tablet of naloxone, suitable for application to the buccal mucosa with rapid drug release for absorption (e.g., within 30 s; Alqurshi et al., in press). Approval has been received from the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK for a first-in-human CTIMP to investigate buccal delivery of naloxone (EudraCT number 2014-001802-16), and the Phase-I trial will generate pharmacokinetics data of naloxone absorption from the buccal cavity in healthy volunteers. This first study is examining absorption of a buccal liquid, and a subsequent study (EudraCT number 2016-000582-23) will examine absorption from the buccal lyophilized formulation of naloxone which we have developed and manufactured (Alqurshi et al., in press) and whose pharmacokinetics will be compared to those with IV and IM injection of the existing licensed naloxone. In this way, we will explore dose comparability and draw a comparison between absorption of buccal naloxone from solution and from the new lyophilized formulation.

4. Discussion

The development of non-injectable formulations of naloxone is of major importance because of the potential for administration by non-medical people in emergency situations. Injectable routes work well and are fit for purpose for use by medical staff in hospital settings or by ambulance personnel attending a community emergency overdose scenario. However, the consideration is different for emergency administration by the general public (i.e. without medical training). While family members can be trained and are regularly given such training and emergency injectable medications for other potential medical crises (e.g., adrenaline/epinephrine for allergy anaphylaxis, insulin for diabetics, etc.), there would nevertheless be greater ease of distribution and comfort with emergency administration if an effective and reliable non-injectable formulation of naloxone was available.

Examination of the extensive list of more than 100 different routes of administration identified three plausible non-injectable routes – nasal, sublingual and buccal – which warrant proper study. If successful, all three routes could become viable, cost-effective future alternatives to the licensed naloxone injection and could facilitate effective bystander response to opioid-overdose while minimizing associated risk.

Consideration and investigation of nasal naloxone is the more advanced area. After a decade of community provision of improvised naloxone nasal spray, several pharmaceutical companies have recently been developing and testing purpose-made naloxone nasal sprays.

In November, 2015, FDA approved a first concentrated naloxone nasal spray (FDA, 2015) and granted fast-track review to a new drug application for a subligual naloxone spray (FDAnews, 2015). In the US at least, the new concentrate nasal product is expected to replace improvised nasal kits which – despite lack of regulatory testing

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or evidence of bioavailability – had been introduced in growing numbers since the late 2000s.

Sublingual medications have been used in medicine to great benefit in emergency situations, such as glyceryl trinitrate (GTN) sublingual tablets or spray as acute treatment of angina or myocardial infarct. However, the sublingual route may be compromised if there is vomit or secretions.

No human data exist for buccal naloxone to date, and study of the buccal route for naloxone administration is less advanced. However, the buccal route has been successfully used to develop non-injectable versions of other medications previously available as injection only. Buccal midazolam ('Buccolam') produces rapid onset of action and its bioavailability (80%) is slightly superior to nasal midazolam (73–75%; Dale et al., 2006; Knoester et al., 2002; Schwagmeier et al., 1998; Taylor et al., 2008). Buccolam is now a licensed treatment that parents can administer while awaiting professional medical care (MHRA, 2011). There have also been promising experimental results with buccal naltrexone delivery in humans (Paderni et al., 2013).

With regard to feasibility of the three candidate routes (see also Table 1), we consider the nasal route to be strong if concentrated solutions are used and provided dose-titration schedules can be made possible. We consider the sublingual route to be weakest, given that access to the sublingual mucosa may be obstructed in at least two scenarios: a) if the mouth of the overdose victim is closed and/or b) if vomiting has occurred. We consider the buccal route to hold real potential if rapid absorption and good stability can be achieved.

The main strength of this review lies in the methodological approach of its exhaustive consideration of all FDA-recognized routes of administration. However, we cannot rule out the possibility that other non-injectable routes that may in future prove feasible for naloxone administration due to technological advances. The scope of this review is further limited by the lack of empirical data from pre-clinical or clinical studies, which reflects the lack of investment in naloxone product development by science and by the pharmaceutical industry. A particular current failing is the disconnect between clinical innovation and the need for evidence of bioavailability and clinical safety (Strang et al., 2016).

With regard to clinical safety, we suggest that the risk of adverse reactions should be studied for novel formulations. The dosage of any new formulation will need to strike a balance between reversing opioid action without causing severe adverse reactions (Hertz, 2012). Reports of the harm caused by naloxone over-antagonism have been described, and high-dose naloxone formulations with increased risk of over-antagonism may also result in negative attitudes from drug users, as previously reported (Neale and Strang, 2015). Similar to testing of the maximum tolerated dose in cancer treatment, there may be merit in experimental study conducted with opioid-dependent volunteers in order to establish, in a population closer to the relevant target population, the non-response rate, dose adequacy and the speed with which the novel naloxone formulation reverses central opioid action.

At least one study has been conducted using a vulnerable population (i.e. opioid-dependent prisoners) to assess the pharmacodymanics of nasal naloxone (Loimer et al., 1992). However, utmost importance is necessary in design and conduct of studies in opioid-dependent volunteers with attention to the informed consent procedure to ensure that all interested subjects are properly informed and sufficiently protected from potential harm. Community consultation with service user groups has already been initiated to discuss what potential study designs would be feasible and ethically sound.

At a minimum, any licensed new naloxone product should be carefully monitored for potential side effects and non-response rate once it enters the market, and take-home naloxone recipients should be actively encouraged to report any adverse reactions that may occur.

To conclude, deaths from opioid overdose can be prevented through prompt administration of naloxone, and there is increasing pre-provision of naloxone for emergency use by non-medical personnel. However, worldwide, provision is held back by reliance on injectable formulations. From application of the FDA criteria and review of all 112 categories for routes of administration, we identify only three routes of possible non-injectable naloxone administration which meet the FDA criteria: nasal, sublingual and buccal. Improvised nasal naloxone kits have been distributed in many cities, and a first concentrate nasal spray was granted FDA approval in November, 2015, although pharmacokinetic data are still not available in the peer-reviewed domain and inter-individual dose variability needs to be studied. The buccal route may have a different pharmacokinetic profile and may have the advantage of ease of carriage and administration as well as not being obstructed by opiate-induced vomiting. After 40 years of opioid overdose treatment by naloxone injection, non-injectable naloxone products are finally being explored, and nasal, sublingual and buccal routes of delivery warrant proper exploration and testing.

Author contributions

JS and RM drafted the manuscript. RM conducted the database analyses. AA, BF, DT, and PR contributed to the overall work and further development of the manuscript. All authors approved of the final draft of the manuscript.

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Declaration of interests

JS declares that he is a researcher and clinician who has worked with a range of types of treatment and rehabilitation service-providers. JS is supported by the National Institute for Health Research (NIHR) Biomedical Research Centre for Mental Health at South London and Maudsley NHS Foundation Trust and King's College London. He has also worked with a range of governmental and non-governmental organisations, and with pharmaceutical companies to seek to identify new or improved treatments (including naloxone products) from whom he and his employer (King's College London) have received honoraria, travel costs and/or consultancy payments. This includes work with, during past 3 years, Martindale, Reckitt-Benckiser/Indivior, MundiPharma, Braeburn/MedPace and trial medication supply from iGen. His employer (King's College London) has registered intellectual property on a novel buccal naloxone formulation with which all authors are involved. JS has also been named in a patent registration by a Pharma company as inventor of a concentrated nasal naloxone spray. For a fuller account, see JS's web-page at http://www.kcl.ac.uk/ioppn/depts/addictions/people/hod.aspx.

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RM, AA, BF, and PR have no interests to declare except that King's College London (employer of all authors) has registered intellectual

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property on a novel naloxone formulation with which JS, RM, AA, BF, PR, and DT are involved.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.drugalcdep.2016.02.042.

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COMPREHENSIVE REVIEW

International patent applications for non-injectable naloxone for opioid overdose reversal: Exploratory search and retrieve analysis of the PatentScope database

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Q5

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Abstract

Q7 ***Issues.*** *Non-injectable naloxone formulations are being developed for opioid overdose reversal, but only limited data have been published in the peer-reviewed domain. Through examination of a hitherto-unsearched database, we expand public knowledge of non-injectable formulations, tracing their development and novelty, with the aim to describe and compare their pharmacokinetic properties.* ***Approach.*** *(i) The PatentScope database of the World Intellectual Property Organization was searched for relevant English-language patent applications; (ii) Pharmacokinetic data were extracted, collated and analysed; (iii) PubMed was searched using Boolean search query '(nasal OR intranasal OR nose OR buccal OR sublingual) AND naloxone AND pharmacokinetics'.* ***Key Findings.*** *Five hundred and twenty-two PatentScope and 56 PubMed records were identified: three published international patent applications and five peer-reviewed papers met eligibility criteria. Pharmacokinetic data were available for intranasal, sublingual and reference routes (intramuscular, intravenous and subcutaneous). Highly concentrated formulations (10–40 mg mL^{-1}) had been developed and tested. Sublingual bioavailability was very low (F = 1%; relative to intravenous). Non-concentrated intranasal spray (1 mg mL^{-1}; 1 mL per nostril) had low bioavailability (F = 11%). For concentrated intranasal spray formulations (≥10 mg mL^{-1}), bioavailability ranges were F = 21–42% and FIM = 26–57% (relative to intramuscular), with peak naloxone concentrations (dose-adjusted Cmax = 0.8–1.7 ng mL^{-1}) reached in 19–30 min (tmax).* ***Implications.*** *Exploratory analysis identified intranasal bioavailability as associated positively with dose and negatively with volume.* ***Conclusion.*** *PatentScope is a valuable data source but rarely explored. From data integration from different naloxone patent applications, we find consistent direction of development of intranasal sprays to high-concentration, low-volume formulations with bioavailability in the 20–60% range. These have potential to deliver a therapeutic dose in 0.1 mL volume.* [McDonald R, Glende ØD, Dale O, Strang J. International patent applications for non-injectable naloxone for opioid overdose reversal: Exploratory search and retrieve analysis of the PatentScope database. *Drug Alcohol Rev* 2017;00:000-000]

Key words: intranasal, naloxone, pharmacokinetics, opioid, drug overdose.

Introduction

On 18 November 2015, the US Food and Drug Q8 Administration (FDA) gave regulatory approval for a concentrated intranasal (IN) naloxone spray by Adapt Pharma [1], which constitutes the first-ever licensed non-injectable naloxone product. Regulatory approval in Canada followed in October 2016 [2]. The FDA and Health Canada decisions have opened up the possibility, for North America at least, of wider access to naloxone in light of the rising death toll from opioid overdoses [3]. At an estimated 106 000 deaths per annum [4], opioid overdose deaths are also a growing international public health concern. To date, globally, no other non-injectable naloxone formulation has been licensed.

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Effective non-injectable naloxone products would remove the risk of needle-stick injury in medical and community settings. Non-injectable naloxone may offer a particular implementation advantage for take-home naloxone (THN) programs, that is, the pre-placement of naloxone kits with opioid users, families, peers, community police and staff at treatment services, drop-in centres and hostels, where it would likely reduce regulatory obstacles and the current requirement of training laypersons in needle-and-syringe assembly and administration [5]. First proposed in 1996 [6], THN has increasingly been introduced in the past decade, and recent World Health Organization (WHO) guidelines and a UN declaration have called for naloxone access for 'anyone likely to witness an overdose' [7,8]. In response, the FDA, the US Centers for Disease Control and Prevention, National Institute on Drug Abuse and Office of the Assistant Secretary for Health and Human Services sponsored a 2012 stakeholder meeting where key criteria for any novel non-injectable naloxone product were proposed [9,10].

According to the FDA [9], one or more standardised doses of a novel non-injectable naloxone formulation would need to result in plasma naloxone levels (i.e. area under the curve; AUC) comparable with a parenteral dose of at least 0.4 mg. If the bioavailability [(F = 'absolute bioavailability', relative to intravenous; *FIM* = 'relative bioavailability', relative to intramuscular (IM)] of the new product compared with the approved injection is low, then it is unclear if adequate efficacy can be reached. Vice versa, if the bioavailability is unexpectedly high, then this may have implications for the safety profile of the novel formulation. Furthermore, the bioavailability compared with injection would need to be reasonably constant between different individuals. In the emergency situation of opioid overdose, naloxone needs to be absorbed rapidly. Absorption would thus need to be at least as rapid as IM injection, whereby onset of effect starts within 3 to 7 min of administration [8]. The key pharmacokinetic (PK) parameters for a non-injectable naloxone formulation are typically the maximum observed plasma concentration (Cmax) and the time from dosing to peak concentration (Tmax), in addition to bioavailability.

A recent systematic review [11] applied the FDA criteria to the peer-reviewed literature and identified three candidate routes of administration for injection-free naloxone delivery: IN, sublingual and buccal. However, at the time of the FDA approval of the first nasal spray, no results from clinical trials on the new nasal spray were published, and human PK data were only reported in one peer-reviewed publication for an improvised IN naloxone spray formulation (2 mg 5 mL^{-1}), with extremely low bioavailability (F = 4%) [12]. While improvised IN spray devices (administered by attaching a mucosal atomiser device to a pre-filled 2 mg 2 mL^{-1} naloxone syringe) are commonly used in THN programs in some countries (US Centers for Disease Control and Prevention) and a significant number of overdose reversals have been reported [13,14], uncertainties regarding their efficacy have been considered and primarily concern their potential non-response rate and lack of safety data [15–17].

Time lag between research and development activity in the pharmaceutical industry and the publication of relevant data in the peer-reviewed literature is not new: Indeed, more than five decades ago, the discovery and original synthesis of naloxone was first reported in a 1961 patent application [18] before a conference abstract [19] and a full journal article [20] followed in subsequent years.

This exploratory review attempts to close the existing gap in the literature by examining published international patent applications of non-injectable naloxone formulations and contributory PK data. The aims are threefold: (i) to trace the concept and product development by route of administration; (ii) to describe the non-injectable naloxone formulations for which human *in vivo* data are available; and (iii) to compare human PK data reported in the patent applications.

Methods

A three-stage approach has been taken.

Stage 1

The PatentScope database of the World Intellectual Property Organization (WIPO), which contains 58 million patent documents including 3 million published international patent applications [21], was searched for patent applications for non-injectable naloxone formulations. PatentScope was searched for English-language patent applications ('Language: EN') that were registered with any international patent office ('Office(s): all') and contained the search term 'naloxone' within their First Page (default). Only patent applications for non-injectable naloxone that contained human PK data were eligible for inclusion in the analysis [Aims (ii) and (iii)].

Stage 2

The pharmaceutical properties of the non-injectable naloxone formulations and human PK data were extracted from patent applications and summarised. To improve comparability between formulations, dose-adjusted values per 1 mg were generated.

Stage 3. To supplement and cross-check the data obtained in Stages 1 and 2, we also searched PubMed for human PK data for non-injectable naloxone using the Boolean search query '(nasal OR intranasal OR nose OR buccal OR sublingual) AND naloxone AND pharmacokinetics' (see Table S1 for search protocol). These three routes of administration were chosen based on the systematic review [11].

For all three stages, R.M. and Ø.D.G. conducted the PatentScope and PubMed searches, assessed retrieved records for eligibility and extracted relevant information under supervision of the senior authors (O.D. and J.S.).

Results

Stage 1. A PRISMA flow diagram of the selection process of patent applications is shown in Figure 1. F1 Five hundred and twenty-two PatentScope records were identified using the search term 'naloxone' for front-page matches. At this stage, a cross-check was made for known patent applications, and it was found that no entry for the FDA-approved Adapt IN spray product had been captured. We thus additionally searched PatentScope for 'Adapt OR Lightlake'-related entries. In late 2014, Adapt Pharma had bought the global license from Lightlake Therapeutics Inc. to develop and commercialise their IN naloxone spray [22]. After matching for the search term 'Lightlake' (front-page search, English language, all patent offices), this additional search yielded five patent applications, which had not been captured using the search term 'naloxone' because Lightlake had not included the word 'naloxone' on the front page. Consequently, we manually added these five Lightlake patent applications (*n.b.* in the following, we denote these as 'Lightlake' unless we refer directly to the licensed Adapt nasal spray product).

Of the 47 records that remained after removing 480 irrelevant records, 10 were excluded based on their abstract (e.g. active ingredient other than naloxone). The remaining 37 records were downloaded for full-text review and screened for human PK data. Of the 14 patent applications that contained relevant PK data, 11 were excluded for the following reasons: five reported only animal data, and six were duplicates (earlier or later versions of patents containing the same PK data but different patent claims or country of publication). Three published international patent applications were identified as eligible for inclusion: WO/2015/136373, WO/2015/095644 and WO/2012/156317.

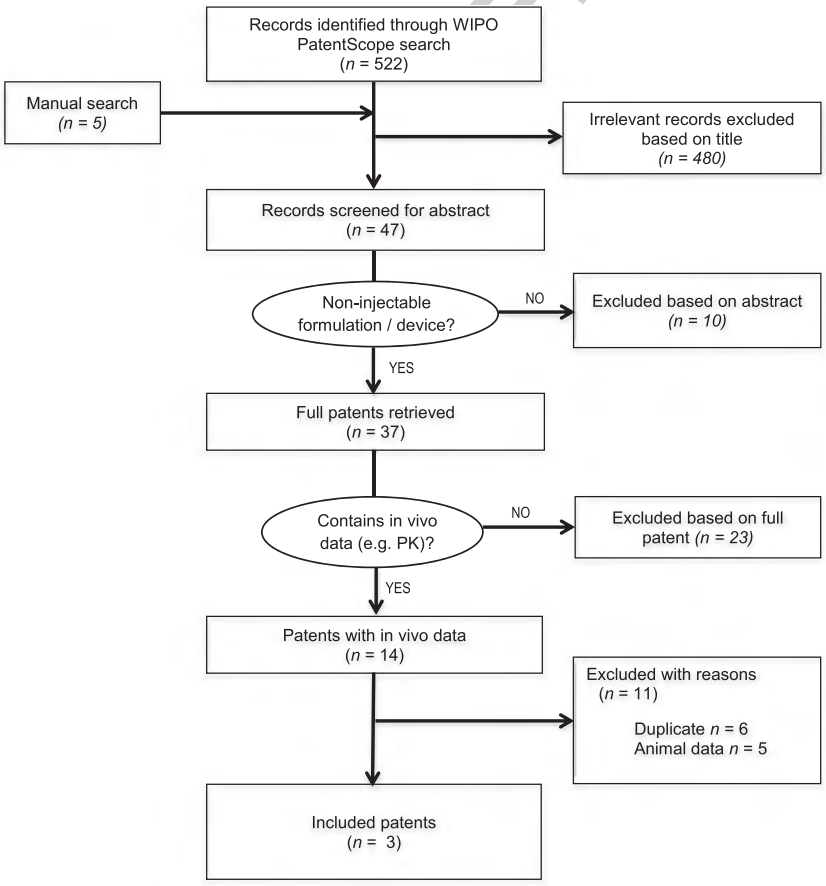

Figure 1. *PRISMA diagram of PatentScope search. PK, pharmacokinetic; WIPO, World Intellectual Property Organization.*

A timeline of the publication of all 37 patent applications (including excluded records) is provided in Table S2 of the Online Appendix. The timeline shows that the concept of non-injectable naloxone (drops, spray, solution, suspension, ointment or gel) was first being explored at the University of Kentucky, with first animal data reported in 1982. The 1990s showed no activity for IN naloxone except for the patent application of a spray dispenser by Britannia Pharmaceuticals in 2000 (*n.b.* the same spray device as in the 2015 FDA-approved Adapt naloxone spray). In 2005, an IN naloxone powder was proposed by the Chinese PLA Academy of Military Science. The first human PK data for IN naloxone were filed by Euro-Celtique in 2012 (WO/2012/156317).

The first patent application describing the concept of sublingual or buccal naloxone was published by the Israeli company Pentach Pharmaceuticals in 2004, and patent applications covering sublingual naloxone (spray, dripping pills) by two Beijing-based companies followed in 2007 and 2011. In 2012, Euro-Celtique included sublingual PK data in its patent application on concentrate IN naloxone spray. In June 2015, INSYS Pharma submitted two patent applications for sublingual naloxone spray (no PK data) and was granted FDA fast-track review later that year [23].

Stage 2: Description of intranasal pharmacokinetic data

We now describe the IN PK data reported in the published international patent applications WO/2015/136373 (Lightlake Therapeutics), WO/2015/095644 (AntiOp) and WO/2012/156317 (Euro-Celtique). The pharmaceutical properties of the naloxone formulations tested by AntiOp (10 mg mL^{-1}) and Lightlake (10, 20 and 40 mg mL^{-1}) are described in detail in Table S4 of the Online Appendix; Euro-Celtique only reported the concentration of their formulations (20 mg mL^{-1}, 40 mg mL^{-1} Naloxone HCl).

All PK data were obtained using cross-over study designs, although sample sizes differed from 7 to 35 subjects per arm. For a full summary of the PK data (including reference routes), please see Table 1. T1

AntiOp described two studies, which are hereby referred to as 'Trial 1 (Pilot)' and 'Trial 2'. AntiOp tested a 10 mg mL^{-1} IN formulation administered as 0.1 mL into one and two nostrils, as well as 0.2 mL per nostril (0.1 + 0.1 mL with 5 min interval). Trial 1 (Pilot) also tested non-concentrate 1 mg mL^{-1} naloxone, with mucosal atomiser device attached to a syringe, thus replicating the improvised IN naloxone distributed off-label in several countries.

Lightlake presented results from two studies: Study 1 assessed a 10 mg mL^{-1} formulation, whereas Study 2 tested 20 and 40 mg mL^{-1} formulations, all administered as 0.1 mL into one and two nostrils (total volume: 0.2 mL).

Euro-Celtique tested IN doses of 8 mg (0.2 mL per nostril; 20 mg mL^{-1} concentration) and 16 mg (0.2 mL per nostril; 40 mg mL^{-1} concentration). Euro-Celtique also included a sublingual arm (16 mg mL^{-1} solution), but this route is not described here in detail, as its absolute bioavailability was only 1%.

For IN administration, we present F as well as FIM, as neither measure was reported across all three patent applications. (Euro-Celtique only provided F, whereas the more recent AntiOp and Lightlake patent applications reported FIM in accordance with guidance from the FDA).

F: For the Euro-Celtique data, we calculated F values of 22% (20 mg mL^{-1}, administered as 0.2 mL per nostril) and 21% (40 mg mL^{-1}; 0.2 mL per nostril) using AUC0-∞ data listed in the PK data appendix of the patent application. We were unable to obtain the higher F values of 32% (20 mg mL^{-1} formulation) and 27% (40 mg mL^{-1}), which Euro-Celtique cited in-text for lower doses (1.2 and 1.6 mg, dose-adjusted from 8 and 16 mg) in the body of the patent application. AntiOp only reported FIM, but included an IV reference in Trial 1 (Pilot), which allowed us to determine the following F-values for comparison: 36% (0.1 mL, one nostril only) and 42% (0.1 mL per nostril) for the 10 mg mL^{-1} formulation, and 11% for non-concentrate naloxone (1 mg mL^{-1} per nostril).

FIM: Lightlake achieved the highest FIM values across all three patent applications, with 0.1 mL of the 10 mg mL^{-1} formulation administered into both nostrils (FIM = 57%). FIM was lower (48%), when the volume of the same formulation was doubled (0.2 mL per nostril). For the 20 mg mL^{-1} formulation, FIM was 54% (0.1 mL, one nostril only) and 55% (0.1 mL per nostril). The 40 mg mL^{-1} formulations achieved 49% and 45% when administered into one and both nostrils, respectively. AntiOp reported the following FIM values for a 10 mg mL^{-1} formulation: 34% (0.1 mL, one nostril only), 31–39% (0.1 mL per nostril) and 26% (0.1 mL per nostril, with re-administration after 5 min; i.e. total volume of 0.2 mL per nostril). Non-concentrate naloxone (1 mg mL^{-1} per nostril) had an FIM of 10%.

t1/2: The terminal half-life (*t1/2*) is the time it takes for the blood concentration of a pharmacological agent to decrease by 50%, which usually translates into the loss of half of its pharmacological activity. Euro-Celtique reported the longest terminal half-lives (t1/2) for IN administration, with 9.1 (40 mg mL^{-1}) and 9.5 h (20 mg mL^{-1}), although data were only available for four subjects. In the AntiOp and Lightlake patent applications, t1/2 fell in the range of 1.2–2.1 h.

Table 1. *Pharmacokinetic properties of patent formulations*

	Study	*n*	Conc.(mg mL^{-1})	Nostrils#	Dose (mg)/volume (mL)	F%	FIM%	tmax(h)
IV	AntiOp Trial 1	13	0.4		0.4/1.0			*0.03 ± 0.1*
	Euro-Celtique	11	1		1.0/1.0			0.85 ± 1.6
IM	AntiOp Trial 1	13	NA		1.0/NA	106[1, 4]		*0.33 ± 0.5*
	AntiOp Trial 2	34	0.4		0.4/1.0			*0.17 (0.1, 1.0)*
	Lightlake 1	14	0.4		0.4/1.0			0.34 ± 0.1
	Lightlake 2	28	0.4		0.4/1.0			*0.42 (0.1, 2.0)*
SQ	AntiOp Trial 1	13	NA		1.0/NA	99[1, 4]	94[1, 4]	*0.17 ± 0.3*
IN	AntiOp Trial 1⋆	13	10	2	2.0/0.2	42[1, 4]	39[1, 4]	*0.42 ± 0.3*
	AntiOp Trial 1⋆	13	10	1	1.0/0.1	36[1, 4]	34[1, 4]	*0.50 ± 0.2*
	AntiOp Trial 1	7	1	2	2.0/2.0	11[1, 4]	10[1, 4]	*0.27 ± 0.1*
	AntiOp Trial 2⋆	33	10	2	2.0/0.2		31[1, 4]	*0.33 (0.3, 0.8)*
	AntiOp Trial 2⋆	35	10	2+2[3]	4.0/0.4		26[1, 4]	*0.42 (0.2, 1.0)*
	Lightlake 1	14	10	2	2.0/0.2		57	0.33 ± 0.1
	Lightlake 1	14	10	2	4.0/0.4		48	0.31 ± 0.1
	Lightlake 2	28	20	1	2.0/0.1		54	*0.33 (0.3, 1.0)*
	Lightlake 2	28	20	2	4.0/0.2		55	*0.33 (0.1, 0.5)*
	Lightlake 2	28	40	1	4.0/0.1		49	*0.50 (0.2, 1.0)*
	Lightlake 2	28	40	2	8.0/0.2		45	*0.33 (0.2, 1.0)*
	Euro-Celtique	11	20	2	8.0/0.4	22)[1, 4]		0.34 ± 0.2
	Euro-Celtique	12	40	2	16.0/0.4	(21)[1, 4]		0.39 ± 0.2
SL	Euro-Celtique	11	16		16.0/1.0	(1)[1, 4]		3.91 ± 10.6

Annotations: Values for tmax, Cmax, AUC and t1/2 denote mean ± SD, except for values in italics. Values in italics denote median ± SD or median (min, max). Inconsistent information between the patent and the PK data whether the formulation contained10 mg mL^{-1} naloxone HCl dihydrate or 10 mg mL^{-1} Naloxone HCl. Dose-adjusted values (per mg) in table are based on Naloxone HCl.
[1]calculated values;
[2]harmonised mean;
[3]re-administration after 5 min;
[4]calculated F and FIM values based on AUC0-∞;
[5]sample size = 3;
[6]sample size = 4. AUC, area under the curve; IM, intramuscular; IN, intranasal; IV, intravenous; NA, not available; SQ, subcutaneous; SL, sublingual.

tmax: IN tmax was 0.27 h (i.e. 16 min) for non-concentrated spray (AntiOp, 1 mg mL^{-1}, 1 mL per nostril) and ranged from 0.31 to 0.50 h (i.e. 19–30 min; AntiOp 10 mg mL^{-1}, 0.1 mL into one nostril and Lightlake 40 mg mL^{-1}, 0.1 mL into one nostril) across concentrated spray formulations.

AUC and Cmax: Dose-adjusted Cmax values (per mg) were highest for the Lightlake 20 mg mL^{-1} formulation administered as 0.1 mL per nostril (Cmax = 1.66 ng mL^{-1}). The same treatment arm achieved AUC0-∞ = 2.48 ng ⋆ h mL^{-1}. The Euro-Celtique 20 mg mL^{-1} formulation reached the highest AUC0-∞ value (2.76 ng⋆h mL^{-1}) and a per mg Cmax of 1.60 ng mL^{-1}. The 1 mg mL^{-1} non-concentrate AntiOp treatment (administered as 1 mL per nostril) had the lowest values (AUC0-∞ = 0.45 ng ⋆ h mL^{-1}; Cmax = 0.27 ng mL^{-1}).

Additional exploratory analyses: In order to examine the potential influence of spray concentration on IN absorption, we plotted AUC, Cmax, and tmax values against volume (adjusted by dose for AUC and Cmax) and dose (Figure 3). For both AUC and Cmax, the plots indicate a positive association with dose and a negative association with volume of the IN spray. The graphs do not suggest a clear association for tmax. F3

Stage 3

The PubMed search generated 56 matches, with zero duplicates (see Figure 2 for PRISMA diagram). Forty-six papers were excluded based on title and abstract (no primary research data from human-subject naloxone studies). F2

The 10 remaining records were then downloaded for full text, with five papers excluded for the following reasons: one was a review article, and four did not include naloxone PK data (see Table S3 for list of excluded studies). The remaining eligible five papers included human PK data in two papers for IN naloxone [12,24] and three papers for sublingual naloxone [25–27]. None of the papers contained human PK data for buccal naloxone.

Table 1. *Pharmacokinetic properties of patent formulations*

	Observed values				Dose-adjusted values (per mg)		
	t1/2(h)	Cmax (ng mL^{-1})	AUC0-∞ (ng * h mL^{-1})	AUC0-last (ng * h mL^{-1})	Cmax(ng mL^{-1})	AUC0-∞ (ng * h mL^{-1})	AUC0-last (ng * h mL^{-1})
IV	*1.28 ± 0.2*	*3.87 ± 2.7*	*1.67 ± 0.5*		*9.68*[1]	*4.18*[1]	
	0.89 ± 0.1[5]	17.9 ± 29.9	12.6 ± 12.4[5]	10.5 ± 7.2	17.9[1]	12.6[1]	10.5[1]
IM	*1.41 ± 0.3*	*2.54 ± 1.0*	*4.43 ± 1.2*		*2.54*[1]	*4.43*[1]	
	1.38 ± 0.3	1.05 ± 0.4	1.67 ± 0.4		2.63[1]	4.18[1]	
	1.21 ± 0.2	0.77 ± 0.2	1.42 ± 0.3	1.38 ± 0.3	1.91[1]	3.55[1]	3.45[1]
	1.19[2]	0.91 ± 0.3	1.83 ± 0.4	1.79 ± 0.4	2.26 ± 0.7	4.57 ± 1.1	4.48[1]
SQ	*1.59 ± 0.6*	*2.72 ± 0.8*	*4.15 ± 1.1*		*2.72*[1]	*4.15*[1]	
IN	*1.53 ± 0.2*	*1.95 ± 1.1*	*3.47 ± 0.8*		*0.98*[1]	*1.74*[1]	
	1.41 ± 0.3	*0.84 ± 0.5*	*1.52 ± 0.5*		*0.84*[1]	*1.52*[1]	
	1.64 ± 0.3	*0.53 ± 0.2*	*0.90 ± 0.2*		*0.27*[1]	*0.45*[1]	
	1.37 ± 0.3	1.78 ± 1.0	2.63 ± 1.3		0.89[1]	1.32[1]	
	1.41 ± 0.3	3.06 ± 1.6	4.42 ± 2.2		0.77[1]	1.11[1]	
	1.19 ± 0.1	2.32 ± 1.0	3.44 ± 1.0	3.41 ± 1.0	1.16[1]	1.72[1]	1.71
	1.22 ± 0.1	4.55 ± 2.9	5.68 ± 1.6	5.63 ± 1.6	1.14[1]	1.42[1]	1.41
	1.70[2]	3.11 ± 1.1	4.86 ± 1.5	4.81 ± 1.5	1.56 ± 0.6	2.43 ± 0.7	2.41
	2.09[2]	6.63 ± 2.3	9.91 ± 2.7	9.82 ± 2.7	1.66 ± 0.6	2.48 ± 0.7	2.46
	2.00[2]	5.34 ± 2.4	8.87 ± 3.3	8.78 ± 3.3	1.34 ± 0.6	2.22 ± 0.8	2.20
	1.91[2]	10.3 ± 4.0	16.1 ± 3.8	15.9 ± 3.8	1.29 ± 0.5	2.01 ± 0.5	1.99
	9.48 ± 3.9[6]	12.8 ± 4.5	22.0 ± 4.2[6]	20.1 ± 4.9	1.60[1]	2.76[1]	2.51[1]
	9.09 ± 2.7[6]	18.3 ± 7.5	42.8 ± 10.6[6]	32.8 ± 10.2	1.14[1]	2.67[1]	2.05[1]
SL	1.13 ± 0.2[6]	0.90 ± 0.4	1.50 ± 0.4[6]	2.67 ± 1.8	0.06[1]	0.09[1]	0.17[1]

Annotations: Values for tmax, Cmax, AUC and t1/2 denote mean ± SD, except for values in italics. Values in italics denote median ± SD or median (min, max). Inconsistent information between the patent and the PK data whether the formulation contained10 mg mL^{-1} naloxone HCl dihydrate or 10 mg mL^{-1} Naloxone HCl. Dose-adjusted values (per mg) in table are based on Naloxone HCl.
[1]calculated values;
[2]harmonised mean;
[3]re-administration after 5 min;
[4]calculated F and FIM values based on AUC0-∞;
[5]sample size = 3;
[6]sample size = 4. AUC, area under the curve; IM, intramuscular; IN, intranasal; IV, intravenous; NA, not available; SQ, subcutaneous; SL, sublingual.

Divergent bioavailability values have been reported for IN naloxone. One healthy volunteers study (n = 6) assessed a non-concentrate formulation of IN naloxone (2 mg 5 mL^{-1}) and reported an absolute bioavailability of only 4%, which the authors attributed as possibly because of the dilute solution (and high volume) used [12]. Higher absorption was reported in a study [24] with recreational prescription opioid users (n = 10) where absolute bioavailability of IN administration of crushed buprenorphine/naloxone (4:1 ratio) of two concentrations (0.5 and 2 mg naloxone) was 24% and 30%, respectively.

Systemic uptake after sublingual naloxone administration was generally found to be low. In one healthy volunteers study, naloxone doses of 1.4 and 2 mg were administered in combination with buprenorphine, resulting in a median tmax of 0.8 h and peak naloxone plasma concentrations below 0.4 ng mL^{-1} for both doses [26]. A second study in non-dependent opioid users (n = 8) [27] assessed escalating naloxone doses (1, 2 and 4 mg) and found that dose-effect comparisons were impossible, as many naloxone plasma concentrations were below the level of quantification (0.050 ng mL^{-1}). The highest individual AUC reported was 0.55 ng * h mL^{-1}.

A third study [25] suggested that sublingual naloxone bioavailability is negatively associated with healthy liver functioning. A sublingual 0.5 mg naloxone tablet (in combination with 2 mg buprenorphine) was administered to 43 subjects stratified by hepatic impairment (mild, moderate or severe), HCV diagnosis without hepatic impairment and healthy volunteers. Across all groups, the median tmax ranged from 0.8 to 1.1 h, with mean t1/2 from 1.9 to 5.5 h. However, the AUC0-last data revealed an approximate 3 to 14-fold increase in total naloxone exposure in subjects with moderate and severe hepatic impairment. Likewise, the naloxone Cmax was 3 to 11 times higher in subjects with hepatic impairment.

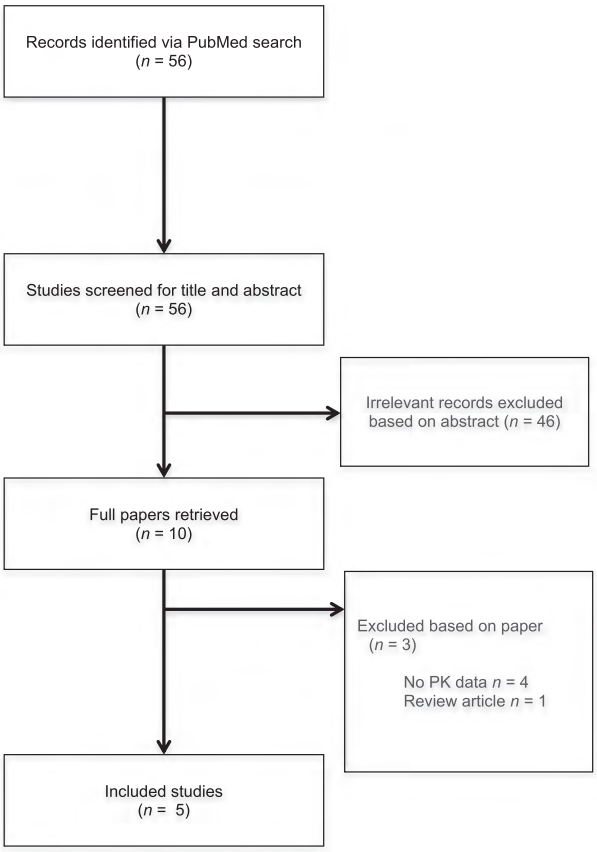

Figure 2. *PRISMA diagram of PubMed search. PK, pharmacokinetic.*

Discussion

Human PK data for purpose-made non-injectable naloxone formulations had not been reported in peer-reviewed scientific papers at the time of the FDA-approval of the first IN naloxone spray [28]. However, published international patent applications by the companies AntiOp, Euro-Celtique and Lightlake contain data on concentrated sublingual and IN spray formulations in the range 10–40 mg mL^{-1}. Through integration of data from WIPO PatentScope and scientific publications retrieved via PubMed, this exploratory review charts R&D activity over the past two decades (particularly 2012–present) and provides an assessment of the current status of non-injectable naloxone development relative to pre-defined regulatory criteria [9,10].

Statement of principal findings

Across all concentrate IN naloxone formulations, bioavailability was 21–42% relative to IV and 26–57% relative to IM. We plotted AUC0-∞ and Cmax values and found a moderately linear relationship with dose (higher dose ➔ higher AUC0-∞, Cmax) and a negative association for volume (lower volume ➔ higher AUC0-∞, Cmax). The highest IN bioavailability (FIM = 57%) was reached when 0.1 mL of a 10 mg mL^{-1} formulation was administered into both nostrils. For the same formulation, FIM decreased to 48% when volume doubled to 0.2 mL per nostril. Volume clearly matters. Also, dose-concentration linearity is evident. We identify the importance of (low) volume with IN bioavailability drastically lower (F = 11%) when a non-concentrate formulation of 1 mg mL^{-1} was administered into both nostrils. This confirms previous reports of low bioavailability (F = 4%) for dilute IN spray (0.4 mg mL^{-1}) [12].

Sublingual naloxone administration of a concentrate solution (16 mg mL^{-1}) had very low bioavailability (F = 1%). This is below the range of 7–9% identified by Chiang *et al.* in their review of sublingual buprenorphine–naloxone formulations [29]. We conclude that sublingual is unlikely to be a route of administration of clinical value.

Strengths and weaknesses of the review

This is the first review of non-injectable concentrate naloxone formulations in the peer-reviewed literature. It includes examination of public-domain information from patent applications. A core strength of this exploratory review lies in the integration of empirical evidence from PubMed and WIPO PatentScope databases, capturing both academic and pharmaceutical industry advances in the field.

The validity of our comparison of IN PK data across different patent applications is strengthened by the similarity of the IN spray formulations used. While Euro-Celtique only disclosed dose concentrations, all formulations all formulations by Lightlake and AntiOp with provided PK data are characterised by absence of absorption enhancers (which increase membrane permeation) and viscosity-increasing agents (which increase the residence time of naloxone to the nasal mucosa and thus contributes to better absorption) (see Table S4 in Online Appendix).

Potential limitations need to be considered. Firstly, not all research and development activity leads to registration of intellectual property or to journal publication, and non-significant or negative results have low likelihood of getting published.

Secondly, our exploratory WIPO PatentScope database search was unlikely exhaustive. Considering that our search initially failed to capture the Lightlake patent applications, we cannot rule out the possibility of other false-negatives. We conducted the default 'First Page' search, which identified any patent document with the search term ('naloxone') mentioned on its cover page,

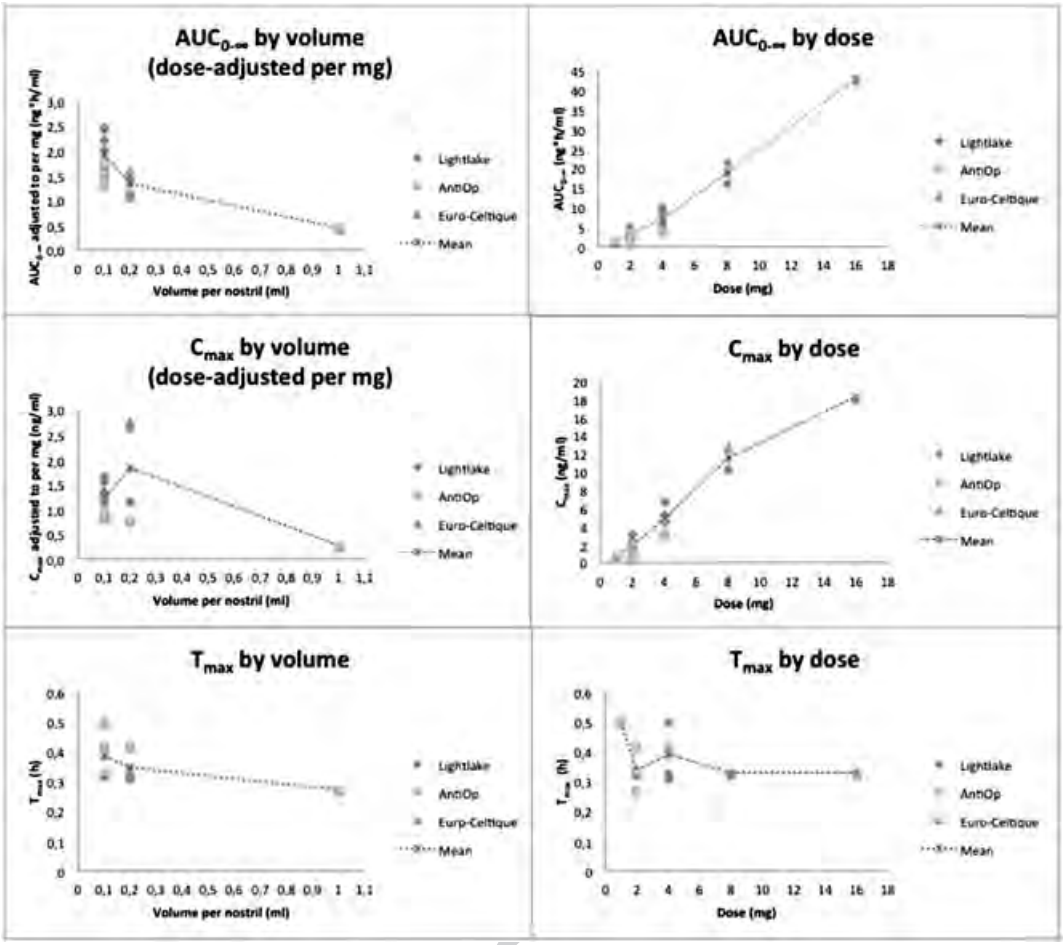

Figure 3. *AUC0-∞, Cmax and Tmax plotted by volume and dose. AUC, area under the curve; Cmax, maximum observed plasma concentration; Tmax;time from dosing to peak concentration.*

generating 522 matches. Had we conducted the more comprehensive 'Full Text' search ('naloxone' mentioned in any full-text patent document), PatentScope would have identified over 19 000 matches, which would have exceeded our capacity for manual screening. Compared with online literature databases such as PubMed or Embase, the functionality of the PatentScope interface is less advanced, in that users cannot export full search results to a citation manager. For every PatentScope entry, we thus had to download associated documents individually to assess eligibility for inclusion in our review. We considered supplementing our PatentScope search with additional query of all national and regional patent offices for which our PatentScope 'naloxone' search had yielded relevant entries (Canada, China, European Union, Germany, Great Britain, Israel, Russia, Singapore, South Africa and United States; see Online Supplement 2). However, we concluded that this was not feasible due to their different search and output formats that are not always compatible with PatentScope: for instance, the British online database Ipsum of the UK Intellectual Property office only permits search by application or publication number (i.e. not by keyword, e.g. 'naloxone') [30], and the United States Patent and Trademark Office offers two separate search modes: one for patent applications (Patent Application Full-Text and Image Database, AppFT) and one for issued patents (Patent Full-Text and Image Database; PatFT) [31], whereas PatentScope does not provide such distinction.

The third limitation concerns the quality of the data retrieved: we did not have access to raw data, and our analysis was reliant upon summary data provided by the patent applicants. Consequently, the comparability of the PK results was limited by different analytical methods and result formats used in the individual studies included in the patent applications (e.g. bioavailability reported as F vs. FIM; central tendency expressed as mean vs. median). For instance, for no apparent reason, we were unable to replicate the F-values that Euro-Celtique cited in-text when we used the PK values listed in the data appendix. Similarly, we remain uncertain about the actual concentration of the AntiOp formulation (10 mg mL^{-1} Naloxone HCl or 10 mg mL^{-1} Naloxone HCl dihydrate), which could have affected calculation

of dose-adjusted values in Table 1. There was also variability in the sampling periods (8–36 h), which may have impacted AUC-dependent measures (e.g. F%, FIM%). In terms of reliability of the mean values reported in Table 1, it also needs to be borne in mind that the cross-over studies (which comprised pilot and registration trials) differed substantially in sample sizes (7–35 subjects per treatment arm).

Meaning of the review: possible mechanisms and implications for clinicians or policy-makers

These findings have multiple implications for clinicians and policy-makers.

IN naloxone. Low spray volume and high concentrations lead to better IN naloxone absorption. Concentrated IN naloxone spray is thus a potentially valuable non-injectable formulation for opioid overdose reversal. This is likely relevant both in medical settings and in the community (THN programs). This conclusion accords with the first FDA-approval of an IN naloxone spray product [1], at 4 mg 0.1 mL^{-1} naloxone hydrochloride (i.e. 40 mg mL^{-1} concentration). However, further examination is required of the full PK curve and the resulting clinical effect because, for all doses of the 40 mg mL^{-1} formulations tested (4–16 mg), we found Cmax (5.34–18.3 ng mL^{-1}) was much higher than for IM references (Cmax = 0.77–1.05 ng mL^{-1}). Consequently, while clinical efficacy of concentrated IN sprays is likely, there is the risk of inducing acute opioid withdrawal in overdose victims [32]. A recent qualitative analysis of heroin/opioid overdose reversals found instances of apparent excessive naloxone dosing and consequent 'over-antagonism', sometimes triggering discharge and active further drug-seeking [33]. Hepatic impairment also increases naloxone bioavailability, particularly relevant when larger fractions of buccal/sublingual or IN naloxone are swallowed [25], potentially causing severe distress and adverse events from naloxone over-antagonism in dependent patients.

The poor IN bioavailability of non-concentrated naloxone using the mucosal atomiser device also raises important questions [15–17]. From a scientific perspective, how can such low absorbed doses be effective if they are indeed succeeding in reversing overdose? Also, the continued use of improvised (i.e. dilute) IN naloxone kits needs review.

Sublingual naloxone. In October 2015, INSYS Therapeutics announced that its sublingual naloxone spray (formulation unknown) had been granted fast-track review by the FDA. Considering the low bioavailability reported by the Euro-Celtique study, it seems unlikely that sublingual naloxone will be clinically useful.

Unanswered questions and future research

Unanswered questions around non-injectable naloxone remain. All PK data reported in the referenced patent applications were from healthy volunteers. It remains unclear how these findings relate to the heroin/opioid users where non-response rates (i.e. response judged by ambulance personnel to need supplementary injected dose) around 18–26% have been reported for IN naloxone [34,35].

Secondly, there are limitations in our current understanding of the PKs and pharmacodynamics of naloxone. While this review largely focuses on the bioavailability of non-injectable naloxone relative to parenteral injection, the absolute naloxone plasma concentration range required to reverse opioid overdose remains unknown. This needs sorting. Because naloxone is a competitive antagonist, the therapeutic dose will likely differ by route of administration alongside inter-individual variability. Moreover, the naloxone dose required to reverse the effects of a specific opioid agonist will depend on the opioid agonist dose and its pharmacological properties, particularly its potency, duration of action and receptor affinity [36].

An ongoing Australian double-blinded randomised clinical trial at the Sydney Medically Supervised Injecting Centre (trial ID: ACTRN12611000852954) compares IN (0.8 mg mL^{-1}) versus IM (0.8 mg mL^{-1}) naloxone treatment and assesses the proportion of suspected opioid overdose cases (by treatment group) needing a second naloxone dose (both groups: 0.8 mg 2 mL^{-1} IM) for overdose reversal. The results of this trial will likely shed light on the question of therapeutic dose.

The 2014 WHO guidelines note that a 0.4–0.8 mg parenteral naloxone dose is effective in most cases to reverse opioid overdose. However, given that the duration of naloxone is shorter than that of many opioids, repeat doses of naloxone may need to be given [37]. The WHO guidelines advise that initial naloxone doses above 0.8 mg increase the likelihood of significant withdrawal symptoms [8]. For any therapeutic drug, dose-related adverse effects (i.e. opioid withdrawal symptoms in the case of naloxone) often occur around Cmax [38], suggesting that novel naloxone formulations with Cmax above that of a 0.8 mg parenteral naloxone injection may pose elevated risk of adverse effects. Future studies should systematically monitor and assess reports of naloxone-related adverse effects (from the medical or

community setting) in relation to the naloxone dose and formulation used.

Thirdly, while the PK data from the patent applications indicated a negative relationship between volume and naloxone uptake, they did not allow us to determine a cut-off for IN spray volume (volume above which naloxone is lost to pre or post-nasal drip). Definition of the maximum volume will affect repeat administrations of IN naloxone spray. This too needs resolution.

Finally, we present a new analytical method of synthesis of public patent data from the WIPO PatentScope database. The limitations discussed earlier illustrate that this exploratory method will require optimisation and would benefit from enhanced functionality of the PatentScope interface, so that review of a greater volume of patent documents would become manageable. A 'Patent Crawler' software has been trialled as a search tool that combines analysis of medication and patent databases [39]. Future open-source editions of such software may potentially help academics, clinicians and members of the general public retrieve medication-related information across patent databases and the peer-reviewed medical literature. If such open-source software becomes available, we hope that our search protocol provided in Table S1 of the Online Appendix will allow researchers to replicate our exploratory analysis with added capture capability. When replicating our search in the future, researchers might also find it helpful to work together with patent experts who will be familiar with the functionality of patent databases and the legal language of (the often broad) patent claims.

In the future, such syntheses would also be more valuable if data were presented uniformly: this would require investigators of non-injectable naloxone formulations (including pharmaceutical companies) to publish their data even if findings are negative (see e.g. AllTrials.net) [40].

Conclusions

Over the past 15 years, IN naloxone sprays have been tested in humans, but no product was licensed and commercially available until late 2015 [1]. With an ongoing epidemic of prescription-opioid overdose deaths alongside a more recent rapid rise in heroin deaths, an IN naloxone spray is finally available to prevent overdose deaths in opioid users—a target population vastly underserved for decades. This first licensed non-injectable naloxone marks a significant milestone towards wider naloxone access and more effective prevention of opioid overdose deaths. High-concentrate IN naloxone has good bioavailability although, thus far, formal product testing has only involved healthy volunteers. It remains possible that high-concentrate formulations may provoke naloxone over-antagonism in opioid-dependent patients. Options for dose-titration and alternative routes (e.g. buccal) also need exploration. We call for proper publication of PK data on naloxone products: only then can there be properly informed consideration of different naloxone products by the clinical, policy and scientific communities.

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Conflict of interest

ØDG was a Master of Science in pharmacy student at NTNU; Norwegian University of Science and Technology, during the conduct of this study. As a part of his master degree, he was involved in the conduct of a clinical trial of an IN naloxone formulation. ØDG is now employed as a pharmacy manager at Apotek 1 Gruppen AS.

OD declares that his employer (NTNU; Norwegian University of Science and Technology) has a Cooperation Agreement with Den norske Eterfabrikk (DnE) Pharma to seek commercialisation of an IN naloxone formulation developed by OD. In this respect, NTNU and its subsidiary Technology Transfer Office and DnE-Pharma also have signed a licensing agreement. The latter regulates potential royalties for OD through NTNU. OD is engaged by DnE as Principle Investigator in a PK study of naloxone for which OD receives no personal honorarium. DnE has compensated OD for project-related travels from Trondheim to Oslo. OD is supported by the The Liaison Committee between the Central Norway Regional Health Authority and the NTNU and by The Joint Research Committee between St. Olav's Hospital and the Faculty of Medicine, NTNU.

JS declares that he is a researcher and clinician who has worked with a range of types of treatment and rehabilitation service-providers. He has also worked with a range of governmental and non-governmental organisations, and with pharmaceutical companies to seek to identify new or improved treatments (including naloxone products), and from whom he and his employer (King's College London) have received research funding, honoraria, travel costs and/or consultancy payments. JS has also been named in a patent application (WO/2012/156317; 'Intranasal

Pharmaceutical Dosage Forms comprising Naloxone') filed by Euro-Celtique S.A. (an Independent Associated Company of Mundipharma Research Limited). For a fuller account of JS's interests, see his personal web-page for King's College London at http://www.kcl.ac.uk/ioppn/depts/addictions/people/hod.aspx. JS is supported by the National Institute for Health Research Biomedical Research Centre for Mental Health at South London and Maudsley NHS Foundation Trust and King's College London.

RM has undertaken an unpaid student industry placement with Mundipharma Research Ltd, with focus on the analysis of naloxone nasal spray formulations. RM is working as a consultant for the United Nations Office on Drugs and Crime (UNODC), supporting a feasibility study of community-based opioid overdose prevention strategies in the framework of the UNODC-WHO Programme on Drug Dependence Treatment and Care (GLOK32). The views expressed in this article are those of the authors and do not necessarily reflect the position of the United Nations.

King's College London (employer for both JS and RM) has separately applied to register intellectual property on a novel buccal naloxone formulation with which JS and RM are involved.

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article.

Table S1. PubMed Search Protocol
Table S2. Timeline of patent registrations
Table S3. Excluded studies (n = 5)
Table S4. Intranasal naloxone spray: Excipients by formulation (per mL)

Pharmacokinetics of concentrated naloxone nasal spray over first 30 minutes post-dosing: analysis of suitability for opioid overdose reversal

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Running head: Pharmacokinetics of naloxone nasal spray

Word count: *2,110 words (excl. references, instructions, etc.)*

Declaration of competing interests:
GM and KS are employees of Mundipharma Research Limited which is associated with Purdue Pharma L.P. under whose auspices the original nasal spray study of abuse liability was originally undertaken. SH is an employee of Purdue Pharma L.P. and was directly responsible for the nasal spray study. JS and RM are employed by the university King's College London (KCL), UK. JS is a researcher and clinician who has worked with a range of governmental and non-governmental organisations, and with pharmaceutical companies to seek to identify new or improved treatments (including naloxone products), and from whom he and his employer (KCL) have received research funding, honoraria, travel costs and/or consultancy payments, including from Mundipharma to KCL for JS' time and input to the study reported above. JS has also been named as an inventor in an earlier patent application filed by Euro-Celtique S.A. (an Independent Associated Company of Mundipharma Research Limited) and entitled 'Intranasal Pharmaceutical Dosage Forms comprising Naloxone'. For JS, see www.kcl.ac.uk/ioppn/depts/addictions/people/hod.aspx. RM has undertaken a student industry placement with Mundipharma Research Ltd, with focus on the analysis of naloxone nasal spray formulations. KCL (employer for both JS and RM) has separately registered intellectual property on a novel buccal naloxone formulation with which JS and RM are involved. JS is supported by the NIHR Biomedical Research Centre for Mental Health at South London and Maudsley NHS Foundation Trust and KCL.

Clinical trial registration details: This manuscript reports on data from a Phase I study conducted in the U.S. in 2004. The study was not registered on ClinicalTrials.gov and therefore does not have an NCT identifier number. Since the study was conducted in 2004, i.e. prior to the U.S. Food and Drug Administration Amendments Act of 2007 (FDAAA, signed September 27, 2007), registration was/is not required.

ABSTRACT (293 words)

Background and Aims: Lack of non-injectable naloxone formulations has impeded widespread take-home provision for the prevention of heroin/opioid overdose deaths. For non-injectable formulations that are finally being investigated, rapid onset of action and sufficient bioavailability will be vital. We present analysis of data from a study of concentrated naloxone nasal spray formulations. Our aims are: to assess 1) pharmacokinetic properties and 2) suitability for overdose reversal in terms of naloxone absorption within 30 minutes post-dosing.

Design and interventions/comparator: Open-label, randomized, 4-way crossover Latin-square pharmacokinetic study of naloxone administration by three routes: intranasal at two doses (8mg/0.4mL, 16mg/0.4mL) versus sublingual (16mg/mL) versus intravenous reference (1mg/mL).

Setting: Clinical Pharmacology Unit at The Ohio State University (Columbus, Ohio, USA).

Participants: 12 healthy volunteers (age 20-41; 7 female).

Measurements: From blood plasma naloxone concentrations, 1) standard pharmacokinetic parameters, including maximum plasma concentration (Cmax) and mean absolute bioavailability (F%, relative to intravenous injection), were determined; as well as 2) partial area under the curve (AUC) values, tmax (time to maximum plasma concentration), and T50% (time to 50% of maximum plasma concentration) as measures of early absorption.

Findings: 1) Bioavailability was F%=25-28% for intranasal naloxone. Sublingual had low bioavailability (F%=2%) and was not considered further. Mean Cmax values for 8mg (12.83ng/mL) and 16mg (18.25ng/mL) intranasal exceeded 1mg intravenous (9.64ng/mL) naloxone. 2) Following intranasal administration, T50% was reached within 8 minutes and tmax within 20 minutes. Mean naloxone absorption from dosing to 30 minutes (AUC30) was greater following 8mg (4.17h*ng/mL) and 16mg (5.91h*ng/mL) intranasal than following 1mg intravenous (1.70h*ng/mL) administration.

Conclusions:
Concentrated naloxone nasal spray has a promising pharmacokinetic profile, with substantial bioavailability. Its early absorption time-course suggests that concentrated nasal naloxone is

suitable for emergency administration in the community, where rapid restoration of respiratory function is essential for opioid overdose reversal.

1. Introduction:

Opioid overdose constitutes a major international public health problem (1). Overdose deaths from heroin and other opioids can be prevented through timely administration of the antagonist naloxone.

Naloxone was, until recently, only licensed as injection. Regulatory criteria for non-injectable naloxone have been proposed (2) and, in 2015/16, a first naloxone nasal spray (4mg/0.1mL) was approved in the US (3) and Canada (4), with 44-47% mean bioavailability relative to intramuscular injection (5).

Some opioid overdoses have insidious onset, while others occur rapidly. Darke and Duflou (6) recently analysed the time course of opiate metabolites post-mortem and concluded that heroin overdose death occurred within 20-30 minutes of injecting in 43% of cases, suggesting the time window for naloxone administration may be very narrow (7). Hence, analysis of naloxone pharmacokinetics in the first 20-30 minutes is particularly important.

In this new analysis of previously unpublished data from a 2004 pharmacokinetic study of naloxone nasal spray (which investigated abuse liability of an oral oxycodone/naloxone formulation), we consider the potential of the studied high-concentration intranasal (IN) naloxone formulations from the different perspective of overdose reversal, with two aims: to assess 1) their pharmacokinetic properties and 2) naloxone absorption in the clinically-relevant period of the first 30 minutes post-administration.

2. Methods:

2.1. Study design:

We report data from a pharmacokinetic study with healthy volunteers conducted in 2004 by Purdue Pharma LP (US). Ethics approval was granted by the Western Institutional Review Board (Olympia, WA, US). Its key features (eligibility criteria, etc.) are summarised in the web-appendix. Participants received naloxone in four dose/route combinations (one per session) in a 4-way crossover Latin square design. The four naloxone sessions compared 1mg/mL intravenous (IV) reference with 16mg/mL sublingual (SL) administration and two IN doses: 8mg/0.4mL from 20mg/mL and 16mg/0.4mL from 40mg/mL solution.

Naloxone hydrochloride 10mg/10mL vials for 1mg/mL IV bolus injection were obtained from Bristol-Meyers Squibb (USA). The SL dose (16mg/mL; prepared from naloxone-hydrochloride powder (Mallinckrodt Pharmaceuticals, USA) in 0.9% sodium-chloride solution) was administered by having subjects retain the solution under the tongue for 5 minutes. IN solution was prepared by dissolving naloxone-hydrochloride powder (see above; 11.0g for 20mg/mL; 22.0g for 40mg/mL solution) in sodium-citrate stock solution (9.35g for 20mg/mL; 20.9g for 40mg/mL) and brought up to 500mL volume using 0.9% sodium-chloride solution. IN solution was atomized using metered dose nasal spray devices (comprising a pump spray assembly threaded onto small amber glass bottle), with two 0.1mL aerosol actuations delivered per nostril, for a 0.2mL total volume per nostril. Subjects were required to remain upright (seated or standing) with the head tilted slightly forward from dosing until 4 hours post-dosing. Pharmacokinetic blood samples were drawn into tubes containing the anticoagulant K_2EDTA. Blood was collected pre-dosing and at minutes 1, 2, 4, 10, 30, 40; and hours 1, 2, 4, 6, 8, 12, 16, 24.

Bioanalysis was conducted by Purdue Pharma L.P. (Ardsley, NY, USA). Naloxone plasma concentration was determined by a validated liquid extraction method using liquid chromatography–mass spectrometry (LC-MS/MS). The range of quantification was 0.01-1.0ng/mL. Concentrations below the limit of quantification were set to zero for pharmacokinetic calculations.

2.2. Outcome measures for this new analysis

Our interest was the potential of IN naloxone for opioid overdose reversal, and consequently we focused on the pharmacokinetics within the first half-hour, examining plasma naloxone sample concentrations from dosing to 30 minutes.

Partial area-under-the-curve (AUC) values were determined for these sampling points using Phoenix WinNonlin 6.4. AUC values are expressed as h*ng/mL, i.e. hour(s) times nanograms per millilitre, representing naloxone exposure over time.

We also introduced the exploratory parameter T50%, defined as time from dosing to concentration equal to 50% of maximum plasma concentration (Cmax) (8).

2.3. Statistical analysis:

Inferential statistics were calculated using SPSS Statistics 23. Analysis of variance (ANOVA) was conducted to determine differences in naloxone absorption by treatment arm. Following WHO guidance (9), dose-dependent AUC data were log-transformed to allow for normal

distribution in the ANOVA. Tukey's HSD test was used for post-hoc comparisons, with significance level at $p<.05$.

3. Results:

3.1. Study participants and sensitivity analysis

Twelve eligible healthy subjects were entered into the study, which is within the FDA recommendation of 6-36 subjects (10); 5 were males (age 20-41 years, height 165-193cm, weight 74-106kg) and 7 females (19-48 years, 157-168cm, 51-83kg). Subject 12 did not attend the final 8mg IN session, and Subject 7 failed to attend the 16mg SL and 1mg IV sessions. These three sessions were handled as missing data. The plasma naloxone concentration from Subject 3 was clearly anomalous at 20 minutes following IV administration, being 5-9 times greater than adjacent time points (10, 30 minutes) with an AUCt-value (26.85h*ng/mL) four times greater than the group median (6.64h*ng/mL). We have excluded all IV data for this individual. Consequently, values reported below refer to sample sizes of n=10 (1mg IV), n=11 (8mg IN, 16mg SL), and n=12 (16mg IN), unless otherwise specified.

3.2. Pharmacokinetics:

Plasma naloxone concentrations over the first 6 hours are displayed in Figure 1 (left-hand graph) and with expanded depiction of the first 30 minutes (right-hand graph). IV administration (1mg) was characterized by rapid uptake and subsequent decline; whereas SL administration (16mg) showed minimal absorption. Both IN administrations (8mg, 16mg) had similar time profiles, reaching peak concentrations in less than 30 minutes post-dosing. (The 12 subjects' individual plasma-concentration curves are provided as web-appendix).

Pharmacokinetic parameters are shown in Table 1. The two IN administrations (8mg, 16mg) displayed similar uptake, with rapid median tmax of 20 minutes (0.33 h) for both doses. T50% was 7-8 minutes for both IN doses (8mg IN: x=0.12h; 16mg IN: x=0.13h), and hence slower than from IV administration (4 minutes; x=.06h,). Cmax values following 8mg IN (x=12.83ng/mL) and 16mg IN (x=18.25ng/mL) were greater than those following 1mg IV (x=9.64ng/mL). Cmax values following 16mg SL were extremely low (x=0.90ng/mL).

3.3. Bioavailability

Dose-adjusted AUC data (per mg) from IN and SL administrations were compared against the 1mg IV reference. Since comparisons were not possible for missing and excluded

sessions (see Section 3.1), absolute bioavailability was determined for sample sizes of n=9 (8mg IN) and n=10 (16mg IN, SL).

The mean absolute bioavailability (F%) from dosing to last measureable concentration (AUCt) was 2.0% for SL naloxone; hence it was not considered further. IN administration had F% of 27.7% (8mg) and 24.6% (16mg; see Table 2).

Mean bioavailability values for partial AUC at 1, 2, 4, 10, 20, and 30 minutes post-dosing are reported in Table 2, with similar increase over time for both IN doses (8mg, 16mg): >5% at 4 minutes, ≥13% at 10 minutes, ≥20% at 20 minutes.

3.4. AUC30 and nasal dose equivalent to 1mg IV bolus

Observed AUC30 values following 8mg IN (x=4.17h*ng/mL) and 16mg IN (x=5.91h*ng/mL) were greater than following 1mg IV (x=1.70h*ng/mL; see Table 1).

These AUC30 values were dose-adjusted, log-transformed and compared in a one-way, between-subjects ANOVA. AUC30 values differed significantly as a function of naloxone treatment [$F(3,40)=255.11$, $p<0.001$]. Post-hoc tests showed that dose-adjusted, log-transformed AUC30 was significantly higher with IV (x=3.21, SD=0.15) versus both IN concentrations (8mg IN: x=2.68, SD=0.19; 16mg IN: x=2.53, SD=0.18). However, there was no significant difference between both IN concentrations (p=0.230), suggesting naloxone absorption was proportional to IN dose administered.

Hence, with dose-adjusted AUC30 values for 8mg (x=0.52 h*ng/mL per mg) and 16mg IN (x=0.37 h*ng/mL per mg) and 1mg IV (x=1.70 h*ng/mL) (from above observed values), we calculate, for AUC30, the IN-dose equivalent to 1mg IV would be 3.3mg IN (20mg/mL formulation) and 4.6mg IN (40mg/mL).

3.5. Safety

No serious adverse events occurred. Side effects reported after naloxone administration included fainting (3 cases; one each after 8mg IN, 16mg IN, 1mg IV), headache (2 cases) and gastrointestinal symptoms (5 cases). These 10 cases were distributed by treatment as follows: 8mg IN (3 cases); 16mg IN (5 cases); 16mg IN (0 cases); 1mg IV (2 cases).

4. Discussion:

Recent WHO guidelines (11) recommend that, similar to adrenaline/epinephrine for the treatment of allergic shock (12), naloxone should be offered to anyone in the community likely to suffer or witness an opioid overdose ('take-home naloxone', THN). However, the lack of licensed non-injectable naloxone formulations until late 2015 (which continues outside North America) has hindered widespread THN (13-17). Once non-injectable solutions exist, naloxone may be provided more widely.

Our analysis identifies a promising pharmacokinetic profile for concentrated naloxone nasal spray. In 2008, Dowling et al. (18) reported only 4% absolute bioavailability with a nasal spray adaptation of a commercially-available concentration of naloxone (2mg/5mL), although the authors suggested the extremely low bioavailability may be a result of excessive volume at the nasal membrane. In sharp contrast, we now report that, at much higher concentrations (8mg/0.4mL, 16mg/0.4mL), there is a mean absolute bioavailability between 25-28%. Even though originally studied for different reasons, we conclude that concentrated solutions of naloxone administered as nasal spray have bioavailability adequate for overdose reversal.
We also report that, crucially, half of the maximum observed concentration (T50%) was reached within 8 minutes and maximum concentration (tmax) within 20 minutes of IN administration. This time profile suggests that concentrated naloxone nasal spray may be suitable for the reversal of overdoses from heroin and other short-acting opioids (e.g. fentanyl), where rapid restoration of respiratory function within 30 minutes of opioid use may be essential (6).

These results are broadly consistent with the recent paper by Krieter et al. (19) who reported a Cmax of 10.3ng/mL for a 8mg/0.2mL IN dose as well as tmax values of 18-30 minutes and bioavailability of 44-54% (relative to intramuscular reference) for 0.1-0.2mL of 20mg/mL and 40mg/mL IN formulations. However, absence of an intramuscular reference in this study means that a direct bioavailability comparison between the studies is not possible.

We did not find a significant difference between the two nasal formulations in their dose-adjusted naloxone absorption (AUC30). This allowed us to estimate an IN dose-equivalent that would deliver the same naloxone exposure within 30 minutes as the reference (1mg/mL IV bolus injection). We calculate that a nasal dose of 3.3mg (at 20mg/mL) and 4.6mg (40mg/mL) will provide, over the clinically-critical initial 30-minute period, the same AUC over 30 minutes as 1mg/mL IV.

Algorithms exist for injectable naloxone to guide correct initial and repeat dosing (20) but have yet to be developed for IN naloxone. The T50% data suggest that initial IN absorption is delayed compared to the IV bolus, with IN administration taking 7-8 minutes to attain half of the peak concentration (versus 4 minutes for IV), and IN absolute bioavailability only surpassing 10% between 4-10 minutes (see Table 2). If this finding is robust, then lay responders may need to be advised to wait some minutes before administering a second IN dose to avoid risk of precipitating over-antagonism.

Several limitations need to be borne in mind. Some averages were based on low subject numbers (see Table 1). There was also variability in the tmax values for IV administration (median: 4 minutes), due to two outliers at 4 hours. It is unclear if the low SL bioavailability resulted from subjects possibly swallowing the solution. For the nasal route, only a 0.2mL-volume per nostril was tested in this study, meaning that a volume-absorption relationship cannot be determined. Finally, while it is generally assumed that atomization at a droplet size greater than 10μm increases nasal absorption (21), the droplet size distribution was not characterized in this study, and its potential impact on nasal deposition cannot be determined.

We should also give consideration to how quickly the nasal spray versus injectable naloxone can be administered, which then needs to be considered alongside pharmacokinetics-derived speed of onset. For example, in a Vancouver ambulance study, differences in time-to-recovery comparing IV versus subcutaneous naloxone, disappeared when the greater time to establish IV access was accounted for (22).

This data analysis focuses on the clinically relevant first 30 minutes, and it also introduces the measure of T50%. Also, while our findings support good bioavailability in healthy subjects, concentrated naloxone nasal spray has yet to be formally tested in the target population of opioid users.

The emergence of supportive pharmacokinetic data for concentrated IN naloxone, along with approval of a first nasal naloxone spray in North America (3)(4), constitutes a significant advancement for the field, after concerns over off-label use of injectable naloxone-hydrochloride solution as nasal spray sparked a lively debate in early 2016 (8).

The time-lag between the original study conducted thirteen years ago (with its results subsequently archived) and this new analysis warrants concern. This new analysis identifies the potential of concentrated naloxone nasal spray for overdose reversal (hence authorship

of this research report is across academia and industry). There has recently been considerable public investment to conduct healthy volunteer studies of nasal naloxone (19): the field could have progressed faster if there had been awareness of the above data. In future, a mechanism is needed to ensure awareness of relevant data by industry and academia."

5. Conclusion:

Concentrated naloxone nasal spray appears to be a feasible formulation with adequate speed of onset and acceptable bioavailability in the concentrated form. This appears directly relevant to prevention of opioid overdoses in medical settings and in the community (THN). The above data find concentrated nasal spray solutions (at 20mg/mL and 40mg/mL) to have acceptable bioavailability and plasma levels over the clinically-critical first 30 minutes, with moderate uptake from 4-10 minutes onwards. Further examination is required (and is in progress) and dose-titration protocols and repeat-dosing guidance will need development, especially for wider distribution to non-medical persons (family members, peers, drug users themselves). We conclude that concentrated naloxone nasal sprays hold real promise, may enable wider THN provision, and can thereby contribute to the prevention of fatalities from heroin/opioid overdose.

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Table 1: Pharmacokinetic parameters (mean, SD)

Parameter	n	Unit	1mg IV	8mg IN	16mg IN	16mg SL
AUC20	10-12	h*ng/mL	1.24 (0.62)	2.50 (1.35)	3.58 (2.25)	0.11 (0.09)
AUC30	10-12	h*ng/mL	1.70 (0.62)	4.17 (1.68)	5.91 (0.30)	0.22 (0.11)
AUCt	10-12	h*ng/mL	8.83 (4.90)	20.07 (4.93)	32.81 (10.22)	2.67 (1.78)
Cmax	10-12	ng/mL	9.64 (12.66)	12.83 (4.47)	18.25 (7.50)	0.90 (0.37)
T50%	10-12	h	0.06 (0.05)	0.12 (0.06)	0.13 (0.07)	0.24 (0.10)
Tmax^	10-12	h	0.07 (0.03, 4.00)	0.33 (0.07, 0.50)	0.33 (0.07, 0.67)	0.67 (0.50, 36.00)

Annotations: AUC20 = partial area under the curve (AUC) from dosing to 20 minutes; AUC30 = partial AUC from dosing to 30 minutes; AUCt = AUC from dosing to last measurable time point; Cmax = maximum observed plasma concentration; Tmax = time to Cmax; ^median (min, max).

Table 2: Absolute bioavailability (F%) based on partial AUCs (1-30 min. post-dosing) & AUCt

	AUC1	AUC2	AUC4	AUC10	AUC20	AUC30	AUCt
8 mg IN	3.4%	2.4%	6.2%	17.5%	27.6%	33.1%	27.7%
16 mg IN	1.2%	1.7%	5.0%	13.0%	19.5%	23.2%	24.6%

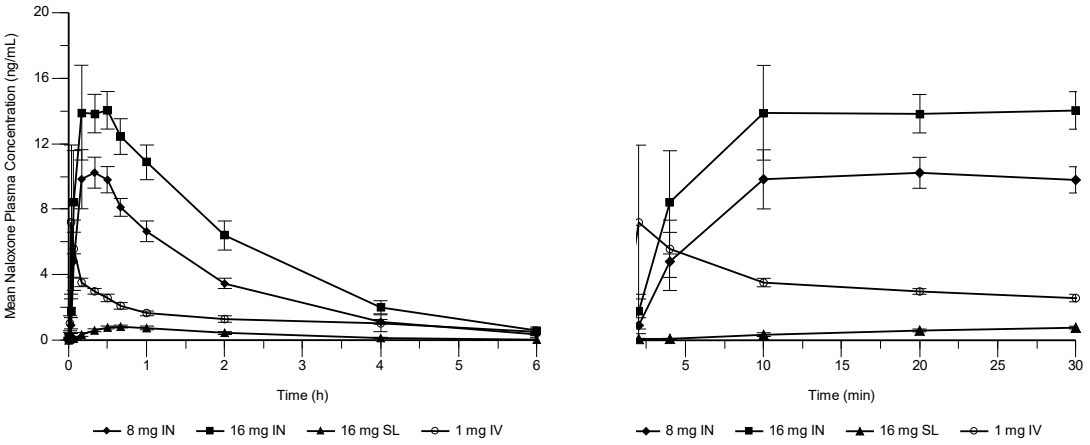

Figure 1 | Mean naloxone plasma profiles within 6 hours (left) and expanded depiction of first 30 minutes (right) post-dosing (excl. Subject 3 IV outlier)

Appendix C. Buccal Naloxone Tablet Patent

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(54) **Title**: NOVEL FORMULATIONS

(57) **Abstract**: A solid formulation comprising an antagonist of an opiate or opioid substance, such as naloxone or a salt or hydrate of said antagonist, in the absence of any opiate or opioid agonist, suitable for buccal administration, for use in the treatment of an opiate or opioid overdose. Novel formulations including in particular instant disintegrating tablets (IDTs) are also described and claimed.

Novel Formulations

The present invention relates to novel formulations of opioid antagonists, in particular naloxone, to kits containing these, as well as to methods for preparing the formulations and their use in therapy.

Background of the Invention

The particularly high mortality amongst heroin users (even compared with users of other illicit drugs) has been recognised in recent years, with the abuse of heroin and other opiates contributing disproportionately to drug-related deaths, and now being one of the major causes of unnatural death amongst adolescents and adults.

Recent research over the last 20 years has also identified that there are specific times of particularly high risk, notably on release from prison and also similarly on release from hospital or residential rehabilitation.

A previous conceptual leap was the realisation that technology routinely used in Accident & Emergency departments, where an emergency intravenous (IV) or intramuscular (IM) injection of naloxone is routinely administered to reverse opiate overdose such as heroin overdose, could be re-conceived as a peer/family-implemented interim emergency action to improve initial interim management of heroin overdose. The pre-provision of take-home emergency naloxone supplies, ready for family/peer-implemented IM injection in the emergency overdose resuscitation situation, was proposed initially as early as 1992, and articulated subsequently (Strang et al., BMJ. (Clinical Research Ed.) 312, 7044, p. 1435-1436).

A study of the feasibility and acceptability to the target population of this proposed approach, studying both treatment samples and non-treatment samples of heroin users (Strang et al., Addiction, 1999, 94, 4, 597-597) and also family members (Strang et al., Drugs: education, prevention and policy (DEPP), 2008, 15:2, 211 - 218) was carried out. The effectiveness of the provision of naloxone training for drug users themselves (Strang et al., Addiction, 2008, 103, 10, p. 1648 - 1657), drug workers (Mayet et al., International Journal of Drug Policy, 2011, 22, 1, p9-15) and family members has also been studied (Williams et al., Addiction, 2014, 109(2), 250-259).

It has been appreciated that the licensed injectable routes (IV, IM, subcutaneous) were far from ideal for non-medical/non-specialist use in this emergency situation (Strang, Addiction, 1999 supra).

However, the oral route is not suitable for naloxone administration, owing to its extensive first-pass metabolism when absorbed from the gastro-intestinal tract. Furthermore the overdose victim is likely to be unconscious.

Nasal administration of naloxone in detoxification methods was first mooted in 1994 and has been the subject of some subsequent studies. It is known that naloxone gets absorbed nasally, at least to some extent. Indeed, since the early 2000s, nasal naloxone has been used by some ambulance services to treat opioid overdose (Barton et al., The Journal of Emergency Medicine. 2005:29(3):265-71) and a purpose-developed naloxone spray was licenced by the FDA in the USA in November 2015. It is quick to administer and reduces risk of needle-stick injury; furthermore, if this fails, an IM or IV dose can be administered from the stock in the ambulance.

CN1565451 describes a naloxone hydrochloride nasal powder formulation.

However, there is uncertainty about how adequately and reliably naloxone is absorbed. A small ambulance-based randomised control trial in Australia compared intranasal (IN) to IM naloxone: the IN group was less likely to restore normal breathing (63% vs 82%) and more likely to require a 'rescue' naloxone injection (26% vs 13%). The group difference of a higher proportion of IN recipients needing a 'rescue' injection (18% vs 5% IM) was also sustained in a replication trial with a more concentrated nasal spray formulation (2mg/mL). This rate is broadly consistent with 16% of opiate overdose victims who did not respond to the initial IN naloxone in a Denver-based observational trial.

The only published report on the pharmacokinetics of intranasal naloxone (Dowling et al. Ther Drug Monit, 2008, 4, 490-6) reported that 'intranasal naloxone had poor bioavailability compared with intramuscular'. Furthermore, they calculated an extremely disappointing bioavailability at only 4% compared with intravenous naloxone.

There is uncertainty about dose adequacy and comparability. The only commercially available naloxone injections have concentrations of 0.4mg/mL or 1mg/mL (adult formulations). Drug administration via nasal spray typically involves giving 0.1mL fluid per nostril, with 0.25mL considered the maximum, as any greater volume is likely lost post-nasally or by nasal drip.

This clearly gives rise to significant dosing issues. Even if a volume of 0.25mL per nostril of the most concentrated available naloxone formulation (2mg/2mL) were

administered, then even assuming that 40% of naloxone is absorbed (discounting the reported nasal bioavailability of only 4%), then the effective IN dose would be 0.2mg, i.e. equivalent to only half the lower recommended injectable dose.

Furthermore, at a practical level, uncertainties about the effectiveness of a nasal spray include: the need for a spray device to function in horizontal position, the impact of compromised nasal mucosa (e.g. chronic ulceration from drug snorting, or obstruction from opiate-induced vomit). Any factors which reduce or delay the nasal absorption of naloxone may lessen the overdose victim's chance of survival.

A more reliable administration route is required, and one which was more compatible with the technical competence and willingness to commit that might reasonably be expected from family members, peer-group, or general public.

Buccal administration was tested in rats as early as 1986 (Hussain M. A. et al., International J. of Pharmacokinetics, 1987, 36 127-130), with a view to developing a suitable administration route for use in conditions such as senile dementia of the Alzheimer's type or as an appetite suppressant in obesity. In this work, various routes of administration were investigated including IV, oral and buccal administration. Oral administration produced very low bioavailability. For buccal administration, solutions of naloxone were administered bucally to rats in which the oesophagus had been ligated. Under these circumstances, high bioavailability was noted. However, liquid formulations are not practicable for buccal administration due to the risk of swallowing or leakage from the mouth/buccal cavity etc., and this route has largely been ignored since.

WO2014/144241 describes complex sublingual or buccal film formulations which may include naloxone but as a formulation in combination with an opioid agonist. In this case, the compositions are designed to provide doses of opioid agonist such as buprenorphine, for use in the treatment of pain whilst minimizing the opportunities for abuse of the dosage form, since the naloxone would produce profound and distressing results if administered intravenously. In this case, the naloxone is included in order to cause distressing effects if the tablet were to be abused by crushing and injecting.

There has been some controversy about whether such compositions, where the main therapeutic agent is buprenophine, when administered sub-lingually, could reverse a heroin overdose (Welsh et al., Addiction, 2008, 103, 7 1226-1228; Nielsen et al., Addiction, 2008, 103, 12, 2065-2066).

Some sub-lingual formulations have also been described in CN1813740,

CN10200037, CN10100755 and Journal of Chinese Pharmaceutical Sciences, 1996, 5 (3).

The applicants have developed a formulation which is specifically intended to address the problems of providing a rapid and readily available treatment for overdoses.

Summary of the Invention

According to the present invention there is provided a solid formulation comprising an antagonist of an opiate or opioid substance or a salt or hydrate of said antagonist, in the absence of any opioid or opioid agonist, suitable for buccal administration, for use in the treatment of opiate or opioid overdose, in particular emergency treatment. In particular, the formulation is for buccal administration.

Buccal administration has advantages even over lingual or sub-lingual administration in the case of opiate or opioid overdoses, since the mode of administration is easy to apply by a third party, even to an unconscious patient. The buccal cavity, being outside the teeth, means that the tablet can be inserted without fully opening the mouth and/or parting the teeth. Once in position, a buccal tablet can remain securely in place. The cheek surface provides a fast-absorption mucous membrane with rapid venous transfer to the brain by virtue of direct venous drainage via the main facial vein. Furthermore, formulations present in the buccal cavity may be better protected from overdose-related vomit or mucous secretions than nasal, lingual or sub-lingual formulations which could be compromised by such vomit or secretions.

As used herein, the term 'solid' refers to non-liquid formulations including semi-solids such as gels and pastes, or amorphous materials below their glass transition temperature, as well as conventional solids.

Suitable antagonists of opiate or opioid substances include naloxone, nalmefene, or naltrexone, or pharmaceutically acceptable salts or hydrates thereof.

In a particular embodiment, the opiate or opioid antagonist is naloxone or a pharmaceutically acceptable salt thereof.

The applicants have found that opiate or opioid antagonists and in particular naloxone may be effectively and rapidly released from buccal formulations, giving rise to a useful and accessible means for treating opiate or opioid overdoses such as heroin overdoses.

The formulations of the invention allow for rapid absorption of the opiate or opioid antagonist into the bloodstream and thence across the blood-brain barrier, from the trans-buccal absorption from the oral vestibular cavity (the cheek pouch) into the facial vein or

other vascular venous drainage and thence directly into the internal jugular vein. As a result, they are able to induce a rapid therapeutic effect in the event of an overdose.

Furthermore, the buccal placement of the formulation will be resilient to impediments and operational obstacles for other routes, (for example, if compared with the nasal naloxone formulations which are currently under investigation or licensed for use) since it would not be compromised by pre-existing nasal ulceration or erosion from drug use. In addition, it would not be influenced by the horizontal posture of the overdose victim, and may be easily placed in the mouth of an individual, even if they are unconscious or prone, by an untrained administrator such as a parent or peer. The administration process would be unlikely to be influenced greatly even if the overdose victim had vomited (a recognised acute opiate-induced effect).

Thus the formulations of the invention provide a useful and novel form of 'emergency' antagonist such as naloxone that is much more compatible with emergency administration by the general public (i.e. by persons not medically trained) than the current injectable forms. Any fear or stigma surrounding the use of an injectable formulation is therefore removed. This opens up, subject to regulatory approval, the option of providing emergency non-injectable antagonist such as naloxone as a medicinal product which might be obtained directly from a community treatment agency or from a community pharmacist, so as to enable wider access and supply for both family and peer group.

In particular, the opiate or opioid antagonist such as naloxone or salt thereof, is the sole active ingredient of the solid formulation, although it may be combined with other opiate or opioid antagonists if required. Suitable salts of naloxone include naloxone hydrochloride. The antagonists may also be in the form of a hydrate such as naloxone dehydrate or the hydrochloride salt, although, generally, the antagonist such as naloxone will be in an anhydrous form after drying.

In a particular embodiment, the solid formulation contains a relatively high dose of naloxone, for example from 0.4mg to 4mg per dosage unit for example from 0.8mg to 3mg per dosage unit. This can ensure that the dosages supplied to the individual are sufficient to mitigate the effect of the overdose.

The solid formulation of the invention is suitably provided in the form of a tablet, lozenge or capsule. In a particular embodiment, the solid formulation comprises a rapid-release formulation such as an instant dissolving tablet, also known as an Instant

Disintegrating Tablet or "IDT", which is particularly suitable for buccal administration. Such formulations of naloxone, sometimes also known as 'orally disintegrating tablets' or 'ODTs' are novel and so form a further aspect of the invention. In particular, the IDT may be shaped so that it fits snugly into a buccal cavity, as described further below.

Such formulations are readily portable and so may be more compatible with being constantly carried on the person, so that the individual who might witness the heroin overdose, or the non-medical person first summoned (e.g. mother, father, sibling, partner) would be more likely to have access to the necessary emergency supply of naloxone, to be able to give an effective dose efficiently. The more realistically portable the product, the greater the likelihood that the naloxone will be readily available for use in an overdose emergency situation.

Furthermore, repeated doses of such formulations if required can be given much more readily than, for example, nasal formulations, where additional doses may provoke further fluid loss, by nasal drip or post-nasal leakage (causing inactivation).

In addition, the solid formulations of the invention show good stability and shelf life. It is known that degradation reactions for example hydrolysis reactions, may occur in solutions including water and that that therefore, formulations such as the current naloxone formulations, I.V. injections and the nasal spray, may have a lower shelf life than solid dosage forms, with much lower amounts of water present, including those of the present invention.

Such tablets are suitably formulated using pharmaceutically acceptable carriers or excipients, such as fillers, diluents, binding agents, plasticising agents, disintegrating agents, flavouring or sweetening agents, stabilisers, antimicrobial agents, cryoprotectants, lyoprotectants, antioxidants, solubilizing agents, tonicifying agents, surfactants, collapse temperature modifiers and inert storage gases for example nitrogen or helium.

In a particular embodiment, the formulation is in the form of a tablet or lozenge which is of suitable size to be easily applied firmly to the inner surface of the cheek, using for example a finger or thumb. For this purpose, the tablet may be somewhat larger than conventional IDTs. For example, the tablet or lozenge may be generally range from 8-35mm in width and length. In a particular embodiment, the tablets will be generally rectangular or square in shape, which the corners optionally rounded or cut. Thus generally rectangular tablets or lozenges may suitably be from 15-35mm long and from 8-20mm wide, for example from 26-30mm or from 26-28mm in length and from 14-17mm

or from 14-18 mm wide, whereas generally square tablets will suitably be from 12-25mm each side.

In a particular embodiment, the tablet has at least one convex surface. For example, the tablet is generally hemispherical in shape with one of the large surfaces of the tablet being flat and the other being convex with slightly bevelled sides as illustrated in Figure 2. This shape allows the tablet to sit comfortably in the buccal area since the hemispherical surface will fit more closely to the profile of the buccal epithelia, producing enhanced contact levels. Furthermore, the flat side makes the tablet easier to handle and apply to the buccal area, for example using a thumb or finger.

The inclusion of a flat side is also very useful as it allows 2 tablets (of the same shape) to be held together firmly and comfortably in the buccal area making a 2 sided spherical tablet of double the dose delivered to one cheek as illustrated in Figure 2B and 2C.

Tablets or lozenges of the invention are suitably relative thin in depth, for example up to 3mm for example from 1-3mm to ensure rapid and complete dissolution when in contact with for example the buccal surface.

The tablet suitably has sufficient adherence properties to ensure that it remains in position throughout the dissolution process. This may be achieved by appropriate selection of excipients used in the tablet production, and in particular a binding agent.

In a particular embodiment, the tablet comprises a binding agent such as a natural polymer, like gelatine, starch, acacia, tragacanth or gum, as well as synthetic polymers such as polyvinylchloride (PVC), polyvinylpyrrolidine (PVP), hydroxypropyl methylcellulose (HPMC), methyl cellulose, ethyl cellulose, or polyethyleneglyclol (PEG), as well as polysaccharides such as glucose, sucrose or sorbitol.

In a particular embodiment, the binding agent comprises gelatine which may be from a variety of sources including cattle, pig, fish and poultry such as chicken. The applicants have found that tablets comprising a significant proportion of gelatine adhere well to damp surfaces and so may be expected to adhere well to a buccal surface.

Furthermore, unlike other buccal formulations of the same category, it does not break down into smaller particles when introduced onto a wet surface. Instead it is held together as one part by the large content of gelatine, while at the same time dissolves rapidly from the side that is in contact with the wet surface. This lowers the chance of swallowing the formulation or, in the case of an unconscious individual, exiting the

buccal/mouth area with any exiting saliva.

Suitably the binding agent is present in an amount of from 40-90%w/w for example from 55-75%w/w of the solid formulation, such as about 65%w/w.

In another particular embodiment, the solid formulation is one which dissolves rapidly, for example in less than 5 minutes and suitably less than 1 minute, when contacted with a moist or damp surface. Rapid dissolution of the tablets can be achieved by various means. For example, as far as possible, generally amorphous materials, including active ingredients or excipients are suitably used in the preparation of the tablets or lozenges. Amorphous structures are generally more prone to disruption than more ordered crystalline or partially crystalline structures. Similarly the tablet or lozenge should have a high level of porosity, which encourages disintegration and dissolution of the tablet.

The choice of excipients will affect how readily amorphous structures may be formed, as will the manufacturing method as detailed more fully below.

A further advantage of gelatine as a binding agent appears to be that, when used in significant quantities as outlined above, it can readily form a highly amorphous matrix for the tablet.

Alternatively or additionally, the formulation may further comprise a disintegrating agent, which ensures that it breaks down rapidly in the mouth. Examples of suitable disintegrating agents include those which liberate carbon dioxide in contact with water so as to actively break down the tablet. Examples of such disintegrating agents include alkali or alkaline earth metal carbonates such as sodium bicarbonate, sodium carbonate, potassium bicarbonate, potassium carbonate or calcium carbonate, as well as citric or tartaric acid or combinations thereof. A particular example of a disintegrating agent is sodium bicarbonate. However, other components such as sugars including mannitol may act as disintegrating agents.

The applicants have found that a particularly preferred combination of agents for use in the formulation is sodium bicarbonate and mannitol. It appears that the sodium bicarbonate or carbonate derived therefrom, for example after freeze drying, inhibits or prevents the crystallisation of mannitol, ensuring that that amorphous character of the product is high.

The amount of disintegrating agent included in the solid formulation will depend upon factors such as the precise nature of the disintegrating agent or combination of

disintegrating agents, as well as the size and nature of the tablet. Typically however, the solid formulation of the invention may comprise from 0-45%w/w. For example, where the disintegrating agent comprises an alkali or alkaline earth metal carbonate such as sodium bicarbonate, it is suitably present in an amount of from 5-15%w/w, for example from 10-12%w/w and suitably about 11%w/w.

In a further embodiment, the formulation of the invention further comprises a filler or diluent. Suitable fillers or diluents for use in the formulations include for example, sugars such as mannitol, lactose, sucrose, trehalose, sorbitol, glucose, or raffinose, or amino acids such as arginine, glycine or histidine, as well as polymers such as dextran or polyethylene glycol (PEG).

If required, the formulation may further comprise a reagent which modulates the absorption profile of the opiate antagonist, for example to increase the speed or level of absorption. Such reagents may include accelerants which increase the speed or absorption of the naloxone or salt thereof, such as a surfactant (e.g. Brij surfactant), or decellerants, which may prolong the delivery of the naloxone, such as a polymer coating (e.g. HPMC) or enteric coating (e.g. methyl acrylate-methacrylic acid copolymers). Alternatively or additionally, the formulation may comprise penetration enhancers such as chitosan, polyethylene oxide, polyvinyl alcohol, polyvinyl pyrrolidone and polyacrylic acid.

Alternatively, a pH adjuster such as a pharmaceutically acceptable buffer may be added to enhance or delay absorption.

In a particular embodiment, where the formulation is intended to use in an emergency overdose situation, the formulation is suitably designed such that each buccal tablet produces a plasma naloxone level which is broadly similar to that of injectable formulations currently in use. For example they may produce a C_{max} plasma level of at least 1000 pg/mL (from 1000 to 5000 pg/mL) with rapid onset of action with T_{max} of from 5 to 30 minutes, and in particular within 20 minutes. Alternatively or additionally, the formulation is designed such that the time it takes for at least 50% of the C_{max} to be achieved (T_{50}%) is 10 minutes or less. This parameter ensures that an adequate amount of naloxone is absorbed quickly, to produce an immediate effect, even if the actual final T_{max} is some time later.

However, additional formulations of the invention may be provided for administration as a supplementary dosage after the immediate emergency has passed, to

ensure a longer and more sustained administration of naloxone. Such formulations will be designed to provide for a later T_{max} or $T_{50\%}$, and/or a longer duration of action, if appropriate, and/or a lower C_{max} plasma level, in accordance with clinical practice.

The solid formulations of the invention are suitably prepared using drying procedures including lyophilisation techniques. In such cases, the formulations may further comprise lyophilisation aids such as cryoprotectants, lyoprotectants and/or collapse temperature modifiers.

In a particular embodiment, the formulation comprises a component such as mannitol, which may act as a lyophilisation aid, as well as a sweetening agent, a binding agent, a structure modifier, a diluent and may also act as a disintegrating agent. Mannitol in particular is known for its hydrophilic nature, bulking properties and is widely used as a cryoprotectant and therefore is usefully included in the formulations of the invention. It may introduce porosity into a formulation. The level however, is suitably selected so that it does not result in significant levels of crystallisation in the formulation. This will depend upon factors such as the nature of the binding agent. However, it is suitably present in an amount of from 10-40%w/w or from 10-50%, in particular from 10-25%w/w and suitably at or below about 24%w/w.

Thus, in a particular embodiment, the formulation comprises a dosage amount such as from 0.4mg to 4mg of naloxone or a salt thereof, distributed throughout an IDT formulation comprising

(a) gelatine in an amount of from 65-69%w/w;

(b) mannitol in an amount of from 20-24%w/w;

(c) sodium bicarbonate in an amount of about 11%w/w;

wherein the formulation is in solid form, and in particular is in solid amorphous form. Such a formulation provides a rapidly available dosage of naloxone, as may be required in an overdose emergency.

The formulations described above are for use in the treatment of an opiate or opioid overdose. The opiate or opioid may be a prescription opiate, where the overdose may be administered accidentally, or an opiate or opioid that is subject to abuse such as heroin.

Certain types of formulation as described above are novel and so form a further aspect of the invention. In particular, the invention further provides a solid formulation in the form of an IDT suitable for buccal administration, and comprising an antagonist of an opiate or opioid substance, or a salt or hydrate of said antagonist.

Suitable antagonists, salts or hydrates are as described above. In addition, excipients are also as described above. In particular, the IDT comprises from 40-90%w/w for example from 55-75%w/w of gelatine or suitably about 65%w/w gelatine.

Yet a further aspect of the invention provides a method for preparing a solid formulation as described above, said method comprising forming a solution of an opiate or opioid antagonist such as naloxone or a salt thereof and at least one pharmaceutically acceptable carrier or excipient, and drying said composition to form a solid formulation.

In a particular embodiment, the drying process is a freeze-drying or lyophilisation process. The lyophilisation process is suitably carried out at temperature in the range of from -20 to -60°C, for example at about -40°C.

In particular, the solution of opiate antagonist such as naloxone or a salt thereof and at least one pharmaceutically acceptable carrier or excipient is frozen before freeze drying or lyophilisation. In particular, the preliminary freezing step is carried out low temperatures, for example at from -10 to -80°C, such as from -20 to -30°C to ensure that freezing takes place rapidly. During a rapid preliminary freezing step, any crystals forming will be quite small, and much of the material will be in an amorphous state. The applicants have found that this leads to a final dried product with high levels of porosity, meaning that the tablets or lozenges will dissolve more rapidly, as discussed above.

Suitable pharmaceutically acceptable carriers or excipients are as described above. In a particular embodiment however, to maximise the amorphous nature of the product, cryoprotectants may be omitted from the formulation.

Suitably the solution is divided into dosage units, in particular tablets or lozenges prior to drying, although if larger volumes of solution are dried, the resultant solid formulation may be formed into dosage units thereafter, for example by compression of powders.

Solid formulations in accordance with the invention and in particular, dosage units in the form of tablets, lozenges, films or capsules, are suitable packaged for storage and distribution. The dosage units may be contained within blister packs, foil packaging or the like, which are suitable for holding individual or small numbers of dosage units and keeping them sterile until required. Suitably the dosage units are packaged in an inert gas such as nitrogen, to avoid premature dissolution of the tablet.

The dosage units may form part of a kit which further comprises elements such as instructions for untrained user, and outer packaging. In a particular embodiment, the kit

comprises a packaged dosage unit, held within a holder which is of the general shape and size as a credit card or other portable devices such as the SwissCard™ or PCMCIA (Personal Computer Memory Card International Association) device, which is provided with a suitable indentation to accommodate the dosage unit. Such holders may be easily kept in a purse or wallet. The holder might further include emergency instructions for the resuscitator, either in written or even voice-delivered form. In this way, it is hoped that individuals who may be susceptible to overdoses, or parents or peers of such individuals, would be able to carry the dosage units with them at all times, so as to be prepared in the event of an emergency.

In a particular embodiment, the kit may comprise one or more dosage units of a first solid formulation for use immediately in an overdose emergency, which provides a short $T_{50\%}$ as described above, and one or more dosage units of a second solid formulation according to the invention which provides a slower or more prolonged drug delivery for subsequent administration.

In a further aspect, the invention provides a method for treating an individual suffering from an overdose of an opioid such as heroin, said method comprising administering to said individual a solid formulation as described above, wherein the administration is by buccal administration. Suitably, the method is carried out immediately signs of an overdose are noticed in an individual. The opportunity for such rapid response whilst awaiting the arrival of the emergency services is designed/intended to improve the prognosis of the individual in such instances.

Detailed Description of the Invention

The invention will now be particularly described by way of example. However, it will be apparent to one skilled in the art that the specific details are not required in order to practice the invention. The following descriptions of specific embodiments of the present invention are presented for purposes of illustration and description. They are not intended to be exhaustive of or to limit the invention to the precise forms disclosed. Many modifications and variations are possible in view of the above teachings. The embodiments are shown and described in order to best explain the principles of the invention and its practical applications, to thereby enable others skilled in the art to best utilize the invention and various embodiments with various modifications as are suited to the particular use contemplated.

The example is illustrated by the accompanying drawing in which:

Figure 1 illustrates a process for preparing an IDT;

Figure 2 illustrates a particular shape of a tablet formulation of the invention where (A) shows a single tablet and (B) and (C) illustrates how these may be held or administered together in a double dose;

Figure 3 shows schematically various formulation holders used in particular embodiments of the invention;

Figure 4 shows the results of differential scanning calorimetry experiments to show the effect of mannitol:gelatin ratio on the thermal properties of the freeze dried instant disintegrating tablets. The tablets were composed of mannitol:gelatin in the ratios illustrated, plus sodium bicarbonate 11% w/w, with the exception of the 100% w/w mannitol sample;

Figure 5 shows the results of Powder X-ray diffraction analysis of tablet formulations in which a) shows the effect of mannitol:gelatin ratio on the solid state properties of the freeze dried instant disintegrating tablets. The tablets were composed of mannitol:gelatin in the ratios specified, plus sodium bicarbonate 11% w/w. (b) shows the powder X-ray diffraction of individual tablet excipients, plus the formulated product with and without naloxone 800 μg;

Figure 6 is a schematic diagram of apparatus used for a digital image disintegration assay, constructed from a blister sheet such as an aluminium blister sheet with a painted black background providing contrast for the tablet. Disintegration of the tablet was monitored as the mean grey value using an image analyser;

Figure 7 is a series of graphs showing the effect of (A) temperature [volume 0.7 mL; medium – phosphate buffered saline], (B) fluid volume [temperature 35°C; medium – phosphate buffered saline], (C) disintegration medium [temperature 35°C; volume 0.7 mL] on the disintegration profile of the naloxone instant dissolving tablet using a digital image disintegration assay. Data represent mean ± standard error, n=3; and

Figure 8 is a graph showing a comparison of the Naloxone instant disintegrating tablet of the invention, compared to a Zydis ® based formulation marketed as Imodium Instant®.

Example 1

Preparation of Naloxone IDT

Gelatine powder BP (0.78g) was first dissolved in hot (70-80°C) water in a 100mL volumetric flask. The solution was swirled until the gelatine was fully dissolved

(10-15 minutes). More water (40mL) at room temperature (18-25°C) was added to the flask with swirling. Then mannitol (10%w/v solution, 2.931g) and sodium bicarbonate powder (0.132g) was added to the solution in the flask and the resultant mixture swirled until all solutes were fully dissolved (10-15 minutes). The flask was then transferred to a water bath held at a temperature of 18-25°C, and retained there until the temperature of solution, as measured by a thermometer, was also between 18 and 25°C.

Naloxone Hydrochloride Dihydrate powder BP (0.0586g) was added to the solution, and the flask swirled until dissolution was complete (5-10 minutes). Thereafter, cold water was added to bring the volume to 100mL and the solution mixed by inverting the flask 3 times.

The resultant solution was poured into 30 individual blister wells (1.5g per well; Figure 1) and frozen in a freezer at a temperature range of -20°C to -26°C over a period of 4 hours to 4 days. The blister wells were transferred into an open polystyrene box of dry ice (≤-70°C) for a period of 2-3 minutes, before individual frozen tablets were transferred from each blister well to an empty type 1 glass bottle using tweezers. The contents of the bottles were inspected to ensure that they had not broken and bottles containing intact frozen tablets were transferred to a freeze dryer.

The freeze-drying chamber was sealed and the cooling unit and vacuum pump were switched on. A temperature of ≤-40°C and a pressure of ≤0.1mbar were maintained for a period of from 96-120hours. At the end of this time, the vacuum pump was switched off and nitrogen gas fed into the freeze-drying chamber at a rate of >50mL min^{-1}. Once the pressure in the freeze drying chamber exceeded 1mbar, the nitrogen feed was closed and drying chamber opened.

The type 1 glass bottles were immediately sealed with rubber bungs whilst still inside the chamber. They were then removed from the chamber and placed on a workbench at room temperature for 30 minutes.

Tablets obtained using this method were of a shape illustrated in Figure 1 and showed a good physical appearance, as they were white and free from damage and erosion. They were weighed and measured and showed good tablet mass uniformity (mean ±5.0%) and uniformity of dimension (length 28.86mm ±5.0%; width 15.99mm ±5.0%.

The naloxone content was checked by HPLC and found to be consistent across the tablets.

A visual disintegration test was carried out by placing the tablets on a tissue, which had been wetted with 0.1M phosphate buffered saline (4mL), at 37-38°C. All tablets were fully dissolved within less than 30 seconds.

Batches were maintained at 4°C or 25°C for periods of from 1 to 6 months and the reviewed again. The results are summarised in the Tables 1a and 1b below.

The tablets obtained showed good uniformity and stability and would be suitable for clinical evaluation.

Example 2

Packaging and Holders

In a particular embodiment, the invention provides a kit comprising one or more solid formulations of the invention packaged in a holder, for example as illustrated in Figure 3A-D.

The holder (1) is suitably constructed of a plastic or polymer such as polyvinyl chloride (PVC), polyethylene, polypropylene, polylactic acid (PLA) or polyethylene terephthalate (PET) or copolymers thereof. However, in a particular embodiment, the holder is an aluminium blister pack as such packaging may be more robust and stable even under hot conditions. It is generally planar in shape. Suitably, the holder is generally rectangular, with a size similar to that of a conventional credit card. For example, the width of the holder is suitably in the range of from 70-100mm, for example about 86mm, with a height of from 40-60mm, for example about 54mm.

Typically, the holder (1) is slightly deeper than a conventional credit card, for example from 2-5mm deep and in particular about 3mm deep. This means that one or more wells or indentations (2) may be provided in the holders, which are adapted to hold tablets such as those produced as described in Example 1. In the embodiment of Figure 3(A), two wells are provided, each adapted to hold a buccal naloxone tablet (2), in particular, 2 tablets formulated for rapid-naloxone delivery, as described above.

Each tablet (2) is sealed within the well, for example using a film such as a plastic or metallic film, in particular an aluminium film, which may be easily broken to access the tablet when required.

If required the film may also be provided with perforations (4), arranged to allow ready fracture of the film to facilitate access to a tablet (2) in a well.

This holder (1) could be retained by a person who may be at risk of overdosing on an opiate, or a peer or relative of such a person, and would provide a means for

administering a dosage of naloxone useful in an emergency situation in the event of an overdose. If the first tablet (2) did not produce a sufficient therapeutic effect, the second tablet (2) stored within the holder may be administered also.

An alternative holder (Figure 3B) includes two wells containing rapid-onset tablets (2) as described above, together with an additional well which holds a tablet (3) formulated for slower and more prolonged release of naloxone. This provides an opportunity to continue treatment for a longer period of time, so that naloxone can continue to be administered, even after the immediate emergency has passed, to ensure that a therapeutic effect can be continued, while emergency services are awaited.

The tablet (3) is of a different size or shape, generally a different size to those of the tablets (2), so that it is easily distinguishable from the rapid-release naloxone formulation. As shown, the tablet (3) is larger than the tablets (2) but it may be smaller if required. It is suitably arranged in a separate section, for example a different quadrant, of the holder (1) to further ensure that the different types of tablet are readily distinguishable, even in an emergency.

A third embodiment of the holder (1) illustrated in Figure 3C comprises a double-pack of the same combination of tablets, with 4-rapid onset tablets (2) located in wells in an upper half of the holder (1), and two follow-up slow release naloxone tablets (3), retained within wells in the lower half of the holder (1). A protective film or foil cover (5) (Figure 2D) is suitably provided over the entire surface of the holder (1), securing the tablets (2, 3) in the respective wells. The film suitably contains appropriately arranged perforations (4) to allow for single tablet removal as well and illustrative explanatory text, to ensure that a user can readily identify the location of the rapid-onset and slow release tablets.

Example 3

Preparation of a range of Tablets

Feed solution for tablet preparation was prepared by disintegrating 0.780 g of pre-weighed gelatin powder (Fagron Ltd, 110 g bloom strength), 0.132 g of sodium bicarbonate powder (Fagron Ltd) and 2.931 g of mannitol 10 (Fresenius Kabi) in 40 mL of water for injection (WFI) held at 70°C. Once all excipients were fully dissolved, a further 40 mL WFI (room temperature) was added and the solution was allowed to cool to room temperature.

Naloxone hydrochloride dihydrate (pharm-grade; Fagron Ltd) 0.0586 g was dissolved in the feed solution, which was made up to 100 mL.

The same method was used to prepare different feed solutions with varying mannitol:gelatin ratios, as summarised in the following Table 1.

Table 1

Equivalent to w/w% composition per tablet			
Composition no	Mannitol	Gelatin	Sodium bicarbonate
1	0.0%	100%	0%
2	0.0%	89%	11%
3	24%	65%	11%
4	44.5%	44.5%	11%
5	89%	0.0%	11%
6	100%	0.0%	0%

The weights of each of the excipients were adjusted accordingly.

Empty wells of an aluminium blister were filled with 1.500 g of naloxone HCl feed solution. The wells were designed to produce tablets which were 29mm long and 16mm wide with a convex lower surface, to provide tablets shaped for easy application to the buccal epithelium of an unconscious patient, for example using a thumb.

Filled blister wells were cooled down to -20°C to allow feed solutions to freeze and then were maintained at -20°C, above its T'g, for a 2 hour annealing step. After annealing, the blisters were cooled down to -80°C. Frozen tablets where removed from the wells and placed into pre-cooled freeze drying vials (1 oz Clear Glass Universal Type 1) packed inside a temperature controlled freeze drying chamber, -40°C, and the drying chamber was sealed. A bench top (Lyotrap freeze dryer; LTE Scientific Ltd) was used to perform the freeze drying cycle. A 5 day freeze drying cycle was initiated to ensure all ice within the tablets was sublimed under $\leq$ 0.01 mbar and $\leq$ -40°C. At the end of the freeze drying cycle, the drying chamber was backfilled with nitrogen, allowing it to reach atmospheric pressure with the cooling unit on. The drying chamber was opened and the freeze drying vials were immediately sealed with rubber stoppers and screw lids while inside the drying chamber. The finished products were removed from inside the drying chamber and inspected for breakage or shrinkage.

Pure mannitol crystalline tablets (composition 6 in Table 1 above) were brittle and difficult to remove from sample vials without collapsing into powder. In contrast, pure

gelatin tables (composition 1 in Table 1) had a sticky texture and lacked porosity. Formulations containing both mannitol and gelatin successfully produced tablets.

The white hemispherical porous tablets were measured with calipers and found to be 29.4 ± 0.2 mm in length, 16.1 ± 0.5 mm in width with a depth of 3.0 ± 0.2 mm and weighed 17.7 ± 0.4 mg. Scanning electron microscopy revealed the pore size in the tablet to have an average length of 0.23 ±0.02 mm(SE) and an average width of 0.094±0.01mm (SE), n=20.

Example 4

Solid state properties of the tablets of Example 3

The solid state properties of the tablets of Example 3 were then investigated using differential scanning calorimetry (DSC) powder X-ray diffraction (PXRD).

Differential scanning calorimetry studies were performed over a temperature range of -40 to 200°C using a DSC Q20 (TA Instruments, New Castle, DE, USA) with a refrigerated cooling accessory (RCS). The DSC cell was purged with 50 cm3/min dry nitrogen and the RCS was purged with 150 cm3/min nitrogen. The DSC cell was calibrated following the instrument manufacturer's guidelines. Experimental conditions for freeze dried tablets followed an equilibration at 25°C for 5 min, ramp to 200°C (10°C/min), followed by a ramp to 25°C (10°C/min) and a ramp to 200°C (10°C/min). Samples were analyzed in aluminium pin-holed hermetic pans. All experiments were repeated three times. The sample size used was approximately 5 mg, with the mass for each experiment recorded accurately on a six-figure balance, (Micro balance: Sartorius UK Ltd).

The results are shown in Figure 4.

PXRD analyses were performed on Rigaku MiniFlex 600 diffractometer (Rigaku, Tokyo, Japan). The samples were spread on a zero background holder and placed on a spinner stage. The instrument produces Cu Kα radiation (1.5418 Å) operated at a voltage of 40 kV and a current of 15 mA over a scan range 3-40° 2θ with a step size of 0.01° 2θ at a speed of 5°/min.

The results are shown in Figure 5. It is clear that addition of gelatin diminished the crystalline melting peak in the freeze-dried product. However, even with quite high gelatin content, persistent peaks were observed in the amorphous halo of the PXRD results. This indicated a crystalline fraction within the freeze-dried tablet and the unique peak at 9.7° 2θ identified the presence of mannitol hemihydrate.

These results show that tablets containing 24% mannitol were in substantially amorphous form.

Example 5

In-vitro Disintegration Studies

A digital image or photographic disintegration assay was developed to measure tablet disintegration in small volumes of medium in temperature controlled blisters and is shown in schematic form in Figure 6. Disintegration was quantified using a gel imager to follow tablet disappearance. The disintegration vessel was a thermal-jacketed aluminium blister sheet with black-painted wells of the same dimension as those used for manufacturing the tablets (Figure 6). Disintegration medium was phosphate buffered distilled water (pH 7.3 ± 0.2) or a synthetic saliva adapted from the SS5 USP recipe for artificial saliva [33], which consisted of distilled water, salts (NaCl = 8 g/L, KH2PO4 = 0.19 g/L and Na2HPO4 = 2.38 g/L) and mucin 2.16 g/L (from porcine stomach).

Assay temperature was adjusted by placing the whole apparatus in a temperature controlled water bath at the target temperature. Disintegration medium, 0.7 mL, was pipetted into the blister wells adjacent to the test well and micro probe thermocouples connected to a data logger thermometer were used to monitor the temperature of the disintegration medium. Once the temperature of the disintegration medium in blister wells reached the target temperature the apparatus was placed inside a heat-insulting box of polystyrene and transferred into a closed box gel imager for the disintegration assay. This apparatus allowed accurate temperature logging throughout the disintegration assay to ensure the temperature of the disintegration medium was maintained ± 1°C of the target temperature.

Disintegration was measured using a GeneSnap version 6.07.03 gel imager, with the camera located above test blister well. A reference image was then taken of test blister well containing disintegration medium, after which the well was dried and an instant disintegrating tablet was placed in the blister. An image of test well was then taken (t = 0 s) and the assay initiated by adding the required volume of temperature-conditioned disintegration medium onto the tablet, (e.g. 0.7mL at 35°C) after which 100 consecutive images were taken at 0.4s intervals. Image J analysis software was used to analyse the images by determining the mean grey value (MGV) corrected for baseline at each time point and normalised to the assay range.

The results are shown in Figure 7. Tablets of the optimized naloxone formulation appeared white but once the disintegration media had been added, a clear solution very rapidly developed revealing the black painted surface of the blister well beneath. For example, adding 0.7 mL of phosphate buffer to a naloxone tablet, with the temperature of the blister well held at 37°C, resulted in approximately half of the matrix remaining at 2s and by 10s the matrix had disappeared, figure 1. For the digital imaging disintegration assay the limit or target for tablet disintegration was classified as the time taken to achieve 10% of the matrix remaining or 90% disintegration. This target was met for the optimized naloxone tablets, under the conditions of 37°C and 0.7 mL, at 4.8 ± 0.6 seconds and furthermore by 10 seconds only 6% of the matrix remained, figure 7a & 7b.

It should be noted that a very small amount of white colour remained in the images recorded at the end of disintegration assay. This was attributed to small air bubbles remaining in the solution and internal reflection at the curved edge of the blister well resulting from the position of the light sources. No particulate matter was seen when the contents of the blister well, from a typical naloxone tablet experiment, were viewed under a light microscope. Even under high magnification only air bubbles in a clear solution were observed. When the phosphate buffer was replaced with artificial saliva, the very small amount of residual white colour was further diminished at the end of the naloxone tablets' disintegration. The surface-active nature of the mucin present in the saliva dispersed the air bubbles, and thus the percentage of matrix remaining fell to a reading of approximately zero, figure 7C.

The novel digital imaging disintegration assay was used to explore the effects of temperature, solvent volume and composition on the disintegration of the tablets. Under all conditions the tablets disintegrated fully (>90%) within 30 seconds. Tablets disintegrated in < 10 seconds in 0.7 mL of phosphate buffer at 35°C (Figure 5a). Temperature variation over the range reported to exist in the buccal cavity, 33-37°C, did not alter the disintegration rate, but the rate was 4-5 times slower at 25°C. In opiate overdose, the volume of oral fluid available in the buccal cavity may be reduced compared to 0.7 mL in a typical adult human. Reducing the amount of fluid available to the tablet progressively reduced the rate at which the tablet disintegrated, with disintegration in 0.1 mL being 4.5 times slower than in 0.7 mL (Figure 7b). Interestingly, when phosphate buffer was replaced with synthetic saliva, a slightly quicker

disintegration rate was observed, a result of better spreading and wetting of the tablet caused by the mucin present in the disintegration medium (Figure 7c).

Evaluating the discrimination between disintegration profiles, measured at different temperatures and volumes, was performed using the similarity factor (f2) test [Shar et al. Pharmaceutical Research, 2010, 49(12) p5854-5862]. This approach was applied because of the high number of data points recorded for each disintegration profile; therefore making other common statistical approaches, for example the MANOVE analysis, impractical. This analysis confirmed that the digital imaging disintegration assay disintegration profiles were sensitive to the volume of disintegration medium used, for example the f2 value comparing between a disintegration volume of 0.7 and 0.4 mL at 35°C was 28.36, (for this statistical approach an f2 value below 50 indicates low similarity or in other words a significant difference between the two profiles of data). Interestingly the profiles at different temperatures, indicated a high similarity for disintegration between 33, 35 and 37°C, as all comparisons had f2 values equal or greater than 50, with only the profiles recorded at 25°C showing a statistical difference to the rest of the data set.

These results show that tablets of the invention are capable of disintegrating in less than 10 seconds, which would be required for the treatment of overdoses.

Example 6

Comparison of tablet of the invention with a commercially available IDT

The methodology of Example 5 was used to compare the tablet of the invention with a marketed freeze-dried and orally disintegrating tablet, Imodium Instant® was investigated using 0.7 mL of phosphate buffer at 37°C.

Imodium Instant® tablets showed slower disintegration compared to the naloxone tablets of the invention, producing a cloudy suspension with 46.0 ± 0.2 % of the matrix remaining after 30 seconds (Figure 8). Light microscopy aided the validation because it showed that the much higher percentage of the matrix remaining, detected in the disintegration assay, was caused by the presence of aggregated particles.

Example 7

Chemical Stability of Tablets of the Invention

The drug content of naloxone HCL/tablet of tablets obtained in Example 3 were checked using a Naloxone HCL HPLC assay (Mostafavi A. et al., Talanta 2009, 77(4) p 1415-1419. The method utilized a C-18 Gemini-NX 5 µm reverse phase column, mobile

phase of 32% v/v methanol HPLC grade and 68% 0.1 ammonium acetate (pH 5.8), isocratic flow rate of 1 mL/min, column temp of 37°C and an injection volume of 20 µL. Absorbance was measured at 229 nm. This was confirmed to be the target 800µg.

The tablets were stored under nitrogen at 4°C or 25°C for nine months, after which the HPLC analysis was repeated. Tablets were found to be stable in that there was less than 5% change in drug content over that time period.

Table 1a | Stability study conducted at 25 ºC

Tests	Spec	Day of manufacture			1 Month			3 Months			6 Months		
		Batch 1	Batch 2	Batch 3	Batch 1	Batch 2	Batch 3	Batch 1	Batch 2	Batch 3	Batch 1	Batch 2	Batch 3
Tablet weight/mg	16.9mg – 20.7mg	18.2	17.1	17.8	18.3	17.3	17.7	18.3	17.3	17.3	18.0	17.0	17.2
		18.1	17.1	18.2	17.9	17.2	17.7	18.3	17.2	17.2	18.1	17.1	17.5
RSD %	≤ 9% deviation	0%	0%	1%	1%	0%	0%	0%	1%	0%	0%	0%	1%
Dimension uniformity test Length	20.0mm – 30.0mm	29.5	29.0	29.5	30.0	29.5	29.5	29.5	29.0	28.5	29.0	29.0	27.5
		29.5	29.5	29.5	30.0	29.5	29.5	30.5	29.0	29.0	29.0	29.0	27.5
Dimension uniformity test Width	14.0mm – 18.0mm	16.0	16.0	16.0	16.0	16.5	16.5	16.0	16.0	16.0	16.0	16.0	16.0
		17.0	15.5	16.0	16.0	16.0	16.0	16.0	16.0	16.0	16.0	16.0	16.0
Disintegration test (n=2)	≤180 sec	19	18	6	6	6	6	7	5	5	9	7	15
Naloxone HCL assay (n=2)	0.76mg – 0.84mg	0.81	0.79	0.80	0.80	0.84	0.84	0.81	0.80	0.81	0.76	0.76	0.76
Pass/Fail		Pass			Pass			Pass			Pass		

WO 2016/146981 PCT/GB2016/050682

Table 1b | Stability study conducted at 4 °C

Tests	Spec	Day of manufacture			1 Month			3 Months			6 Months		
		Batch 1	Batch 2	Batch 3	Batch 1	Batch 2	Batch 3	Batch 1	Batch 2	Batch 3	Batch 1	Batch 2	Batch 3
Tablet weight/mg	16.9mg - 20.7mg	18.2	17.1	17.8	18.4	17.0	17.3	18.5	17.3	17.9	18.4	17.3	17.8
		18.1	17.1	18.2	18.6	17.3	17.4	18.5	17.4	17.6	18.4	17.1	17.8
RSD %	≤ 9% deviation	0%	0%	1%	1%	1%	0%	0%	0%	1%	0%	1%	0%
Dimension uniformity test Length	20.0mm - 30.0mm	29.5	29.0	29.5	29.0	29.0	29.0	29.0	29.0	29.0	29.0	29.5	28.5
		29.5	29.5	29.5	29.5	28.5	29.0	29.0	29.0	29.0	29.0	29.5	28.5
Dimension uniformity test Width	14.0mm - 18.0mm	16.0	16.0	16.0	16.0	16.0	16.0	16.0	16.0	16.0	16.0	16.5	16.0
		17.0	15.5	16.0	16.0	16.0	16.0	16.0	16.0	16.0	16.0	16.5	16.0
Disintegration test (n=2)	≤180 sec	19	18	6	9	9	4	16	9	5	9	6	6
Naloxone HCL assay (n=2)	0.76mg - 0.84mg	0.81	0.79	0.80	0.80	0.83	0.79	0.81	0.81	0.82	0.76	0.78	0.80
Pass/Fail		Pass			Pass			Pass			Pass		

Claims

1. A solid formulation comprising an antagonist of an opiate or opioid substance, or a salt or hydrate of said antagonist, in the absence of any opiate or opioid agonist, for use by buccal administration in the treatment of an opiate or opioid overdose.

2. A solid formulation according to claim 1 wherein the said antagonist is naloxone or a pharmaceutically acceptable salt or hydrate thereof.

3. A solid formulation according to any one of the preceding claims wherein the said antagonist, is the sole therapeutically active ingredient.

4. A solid formulation according to any one of the preceding claims which is in the form of a dosage unit and which comprises 0.4mg to 4mg naloxone per dosage unit.

5. A solid formulation according to any one of the preceding claims which is in the form of a tablet, lozenge, film or capsule.

6. A solid formulation according to claim 5 which is in the form of an instant dissolvable tablet or instant disintegrating tablet (IDT).

7. A solid formulation according to any one of the preceding claims which further comprises a pharmaceutically acceptable binding agent.

8. A solid formulation according to claim 7 wherein the binding agent is gelatine and at least some of the gelatine is in amorphous solid form.

9. A solid formulation according to any one of the preceding claims which further comprises a disintegrating agent.

10. A solid formulation according to claim 9 wherein the disintegrating agent is sodium bicarbonate.

11. A solid formulation according to any one of the preceding claims which further comprises a filler or diluent.

12. A solid formulation according to any one of the preceding claims wherein the filler or diluent is mannitol, at least some of which is in amorphous solid form.

13. A solid formulation according to any one of the preceding claims which comprises a combination of sodium bicarbonate and mannitol.

14. A solid formulation in the form of an IDT suitable for buccal administration, and comprising an antagonist of an opiate or opioid substance, or a salt or hydrate of said antagonist.

15. A solid formulation according to claim 14 wherein the said antagonist is naloxone or a pharmaceutically acceptable salt or hydrate thereof.

16. A solid formulation according to claim 14 or claim 15 wherein the said antagonist is the sole therapeutically active ingredient.

17. A solid formulation according to any one of claims 14 to 16 which comprises 0.4mg to 4mg naloxone per IDT.

18. A solid formulation according to any one of claims 14 to 17 which further comprises from 40-90%w/w gelatine.

19. A solid formulation according to claim 18 wherein at least some of the gelatine is in an amorphous solid form.

20. A solid formulation according to any one of claims 14 to 19 which further comprises a disintegrating agent.

21. A solid formulation according to any one of claims 14 to 20 which further comprises mannitol, at least some of which is in amorphous solid form.

22. A solid formulation according to claim 1 or claim 14 which comprises a dosage amount such as from 0.4mg to 4mg of naloxone or a salt thereof, distributed throughout an IDT formulation comprising

(a) gelatine in an amount of from 65-69%w/w;

(b) mannitol in an amount of from 20-24%w/w;

(c) sodium bicarbonate in an amount of about 11w/w%;

wherein the formulation is in solid form.

23. A solid formulation according to claim 22 which is in amorphous form.

24. A method for preparing a solid formulation according to any one of the preceding claims, said method comprising forming a solution of an opiate antagonist and at least one pharmaceutically acceptable carrier or excipient, and drying the frozen composition to form a solid formulation.

25. A method according to claim 24 wherein the solution of an opiate antagonist and at least one pharmaceutically acceptable carrier or excipient is subjected to a preliminary freezing step prior to drying.

26. A method according to claim 25 wherein the freezing step is carried out at a temperature of from -10 to -80°C.

27. A method according to any one of claims 24 to 26 wherein the solution is divided into dosage units prior to drying.

28. A method according to any one of claims 24 to 27 wherein the drying process is a freeze-drying or lyophilisation process.

29. A kit comprising a solid formulation according to any one of claims 1 to 23 which is contained within a sealed package.

30. A kit according to claim 29 wherein the package is contained within a holder suitable for storage in a purse or wallet.

31. A kit according to claim 29 or claim 30 which comprises one or more dosage units of a first solid formulation for use immediately in an overdose emergency, and one or more dosage units of a second solid formulation according to any one of claims 1 to 23 which provides a slower or more prolonged drug delivery for subsequent administration.

32. A method for treating an individual suffering from an overdose of an opiate or opioid, said method comprising administering to said individual a solid formulation according to any one of claims 1 to 23, wherein the administration is by buccal administration.

33. A method according to claim 32 wherein the opiate or opioid is heroin.

Figure 1

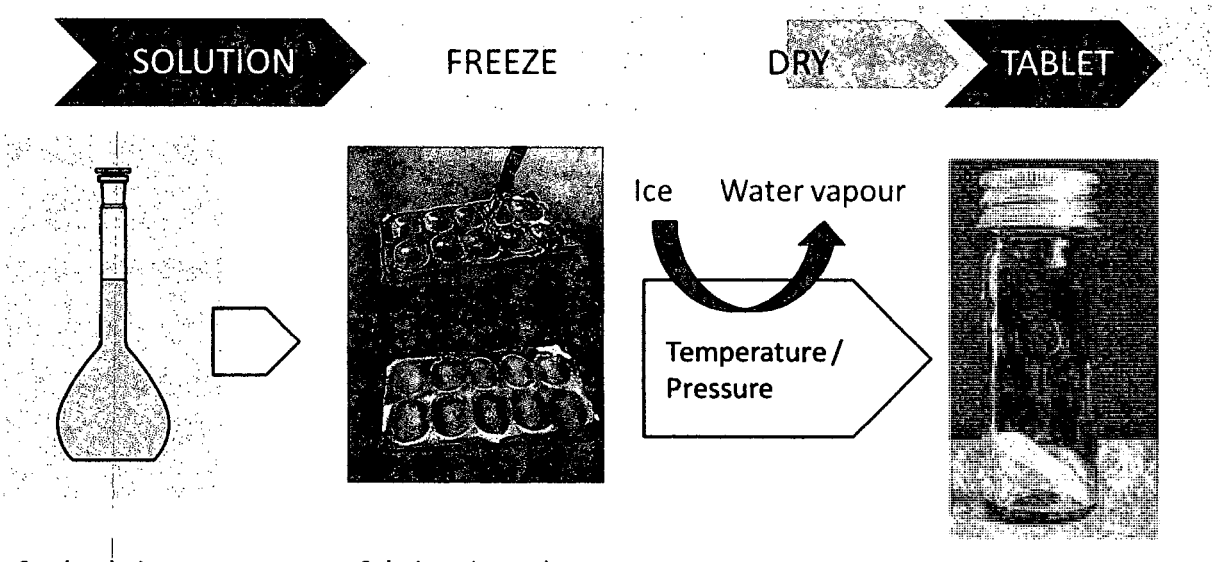


Figure 2

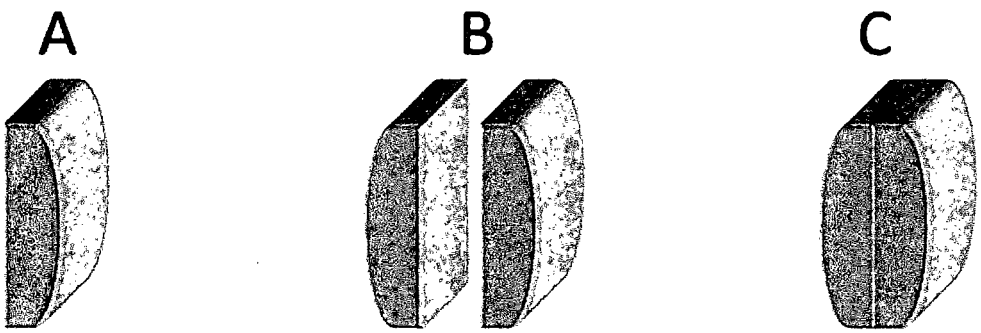


Figure 3

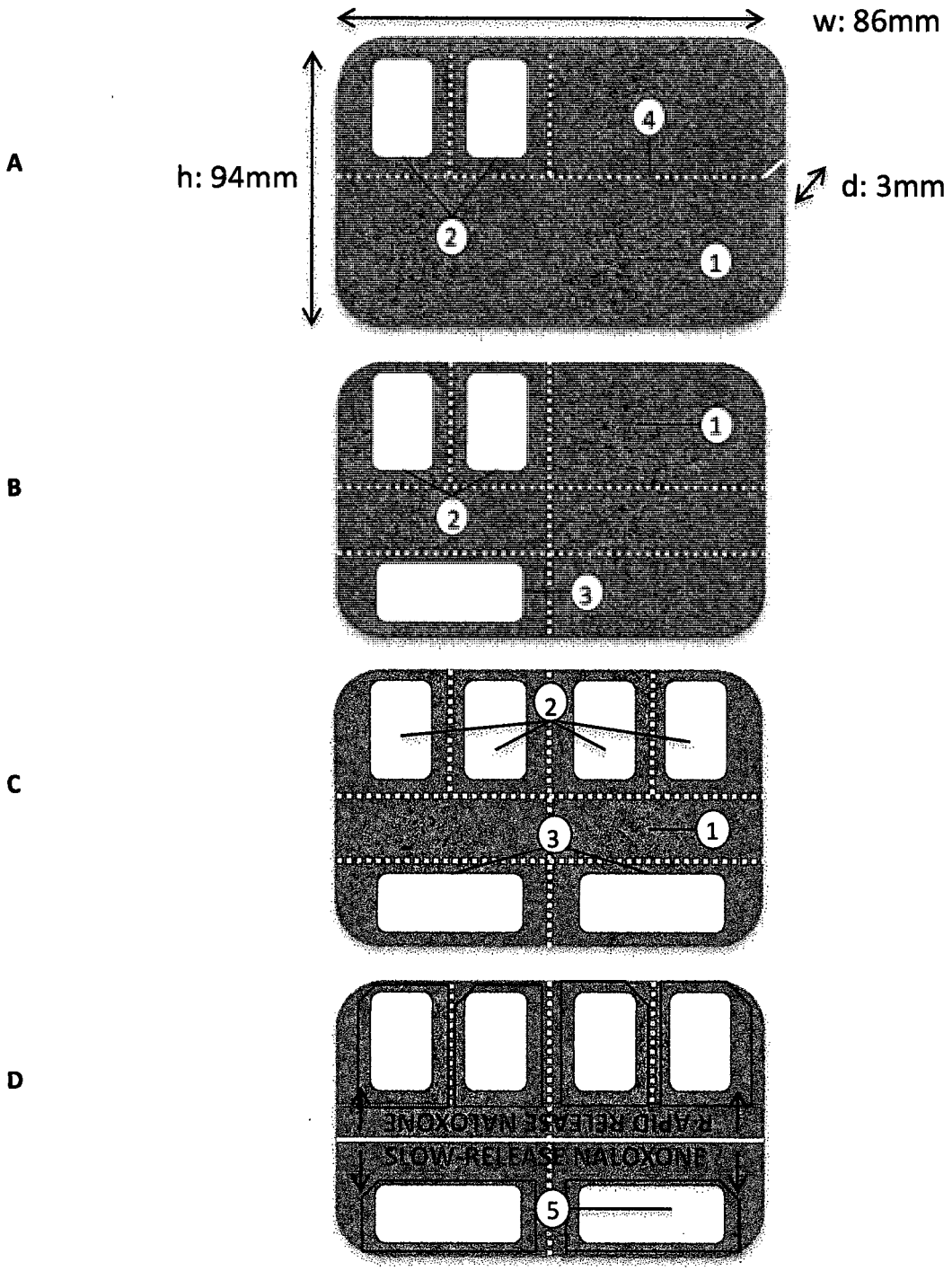

A
w: 86mm
h: 94mm
d: 3mm
4
2
1
B
1
2
3
C
2
3
1
D
RAPID RELEASE NALOXONE
SLOW-RELEASE NALOXONE
5

Figure 4

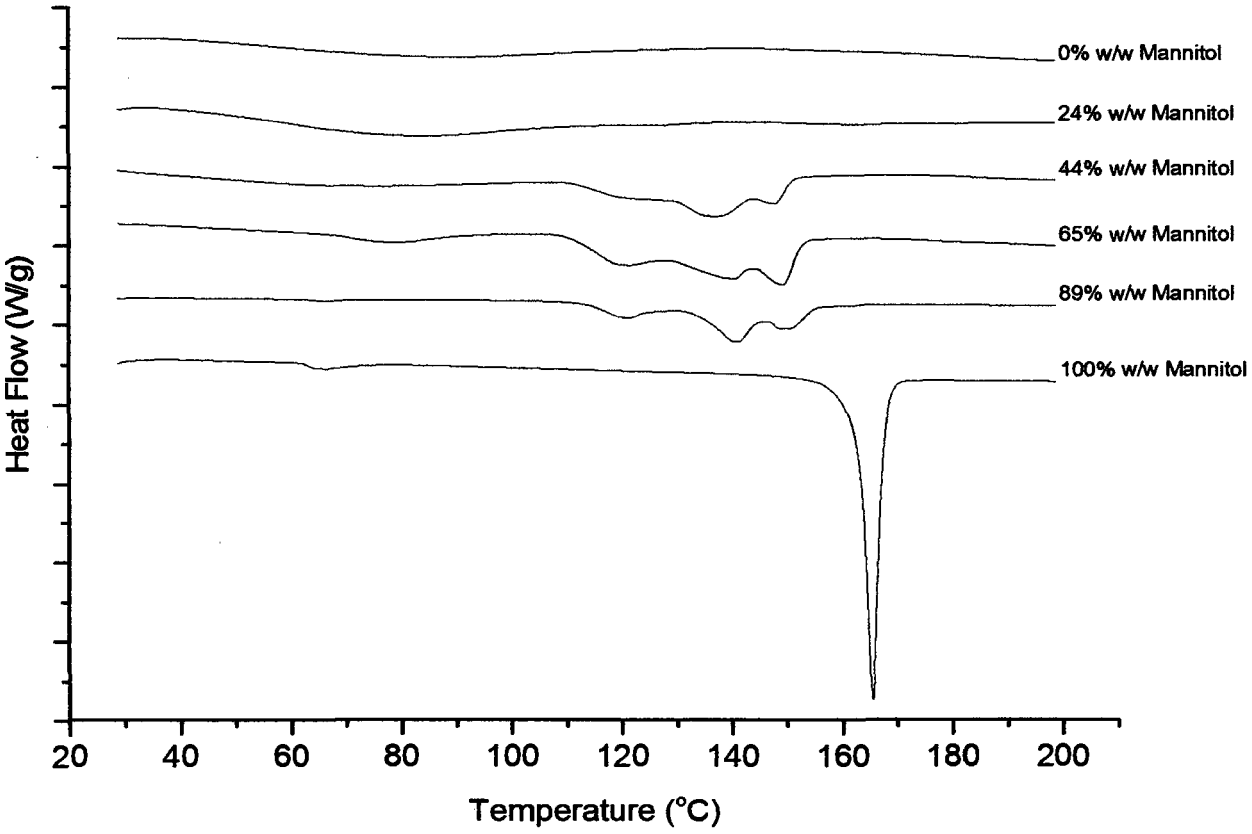
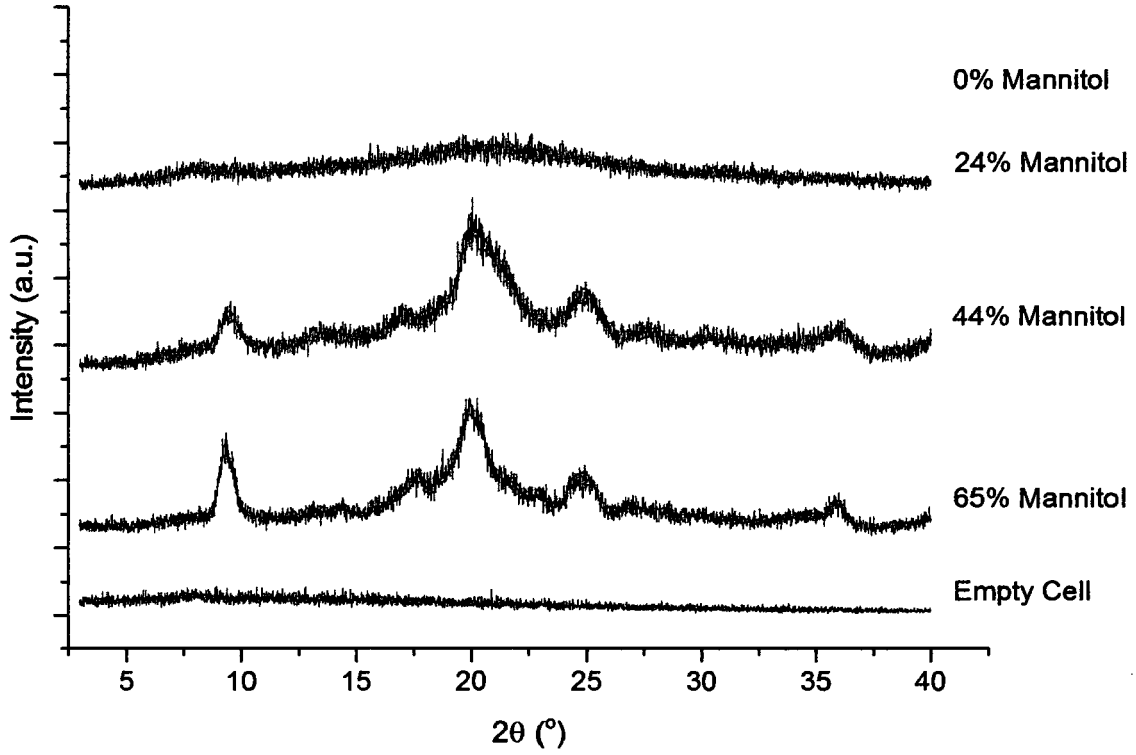

0% w/w Mannitol
24% w/w Mannitol
44% w/w Mannitol
65% w/w Mannitol
89% w/w Mannitol
100% w/w Mannitol
Heat Flow (W/g)
20
40
60
80
100
120
140
160
180
200
Temperature (°C)

Figure 5


0% Mannitol
24% Mannitol
44% Mannitol
65% Mannitol
Empty Cell
Intensity (a.u.)
5
10
15
20
25
30
35
40
2θ (°)

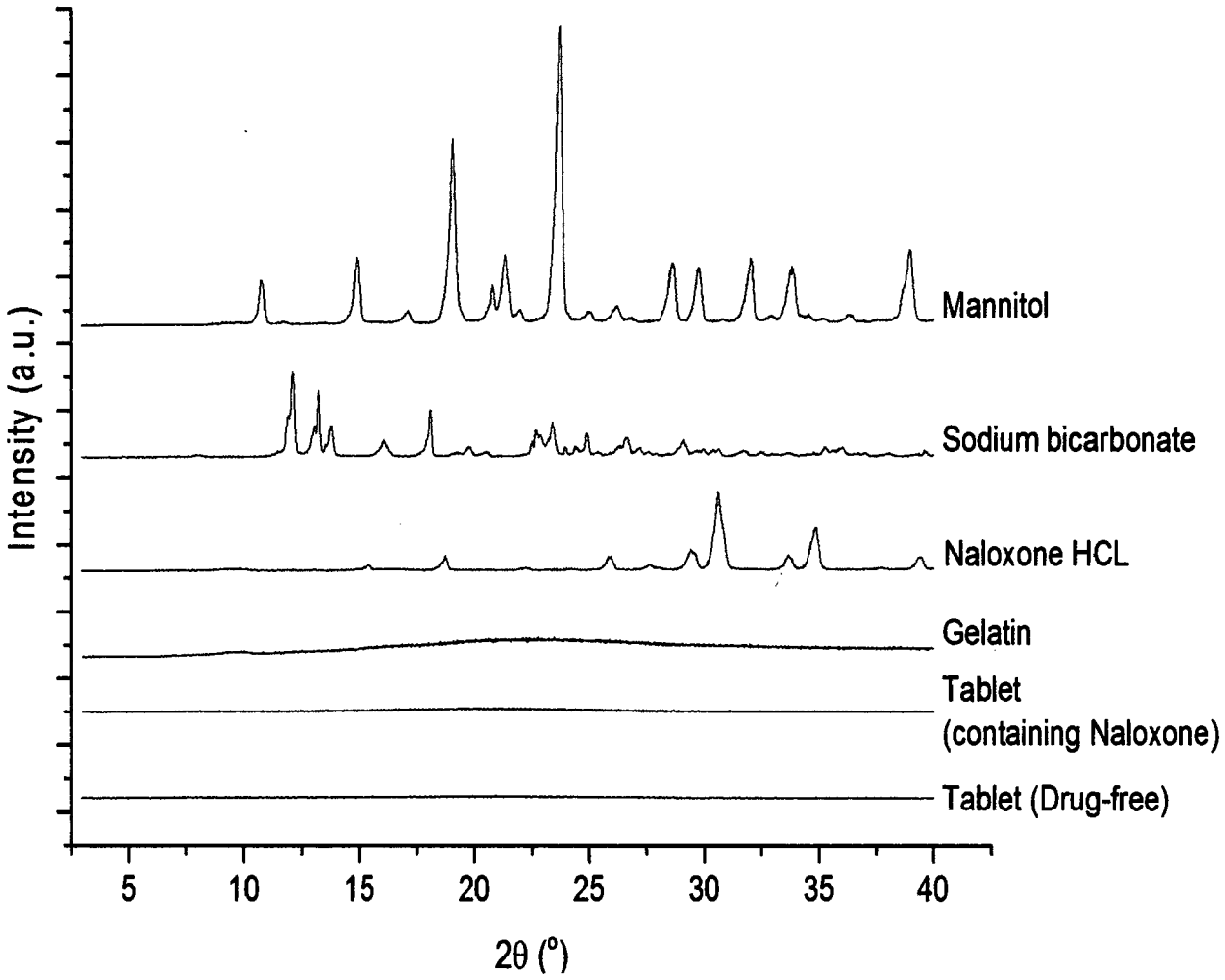

Mannitol
Sodium bicarbonate
Naloxone HCL
Gelatin
Tablet
(containing Naloxone)
Tablet (Drug-free)
Intensity (a.u.)
5
10
15
20
25
30
35
40
2θ (°)

Figure 6

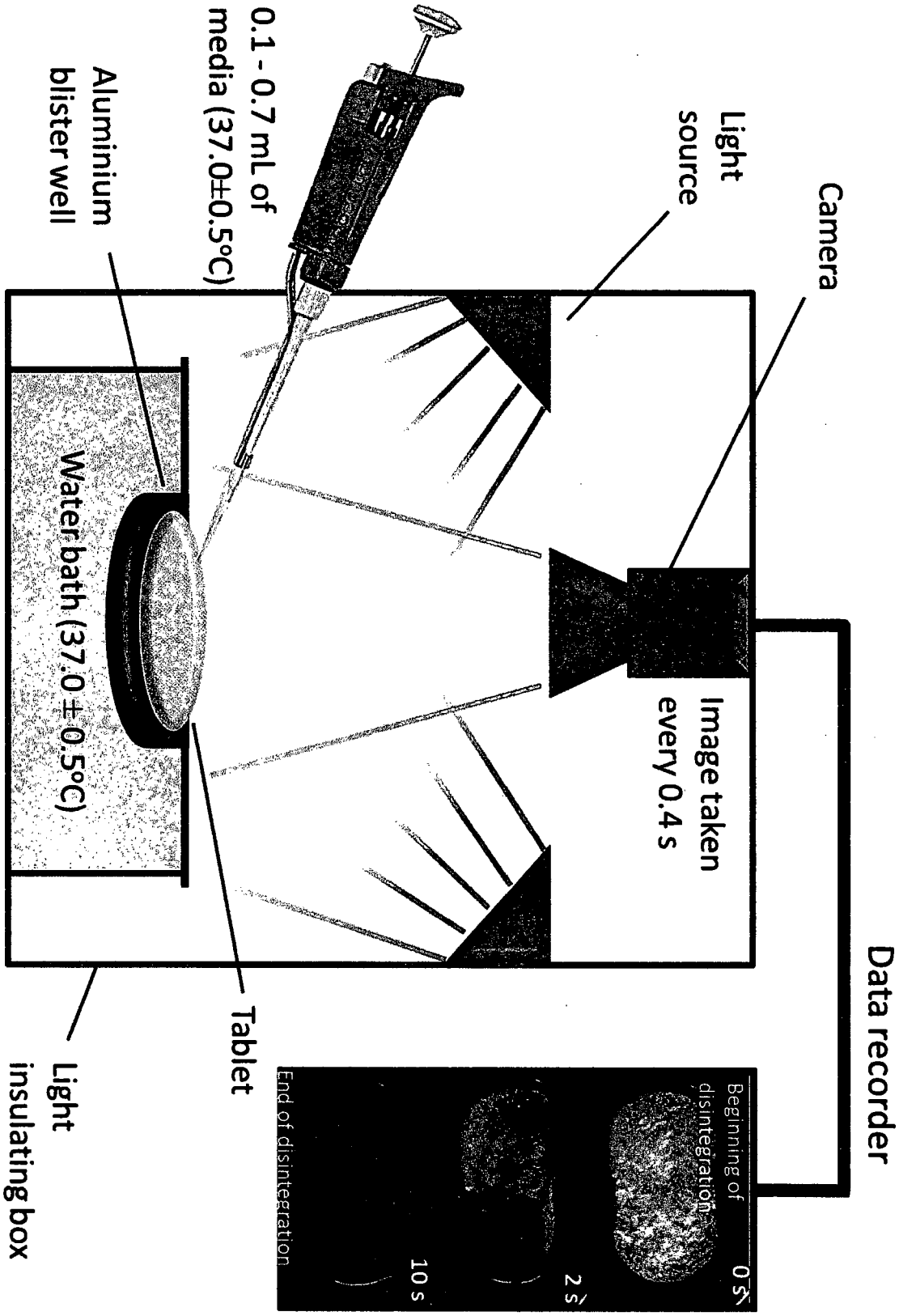

0.1 - 0.7 mL of media (37.0±0.5°C)
Aluminium blister well
Light source
Camera
Water bath (37.0 ± 0.5°C)
Image taken every 0.4 s
Data recorder
Tablet
Light insulating box
Beginning of disintegration
0 s
2 s
10 s
End of disintegration

Figure 7

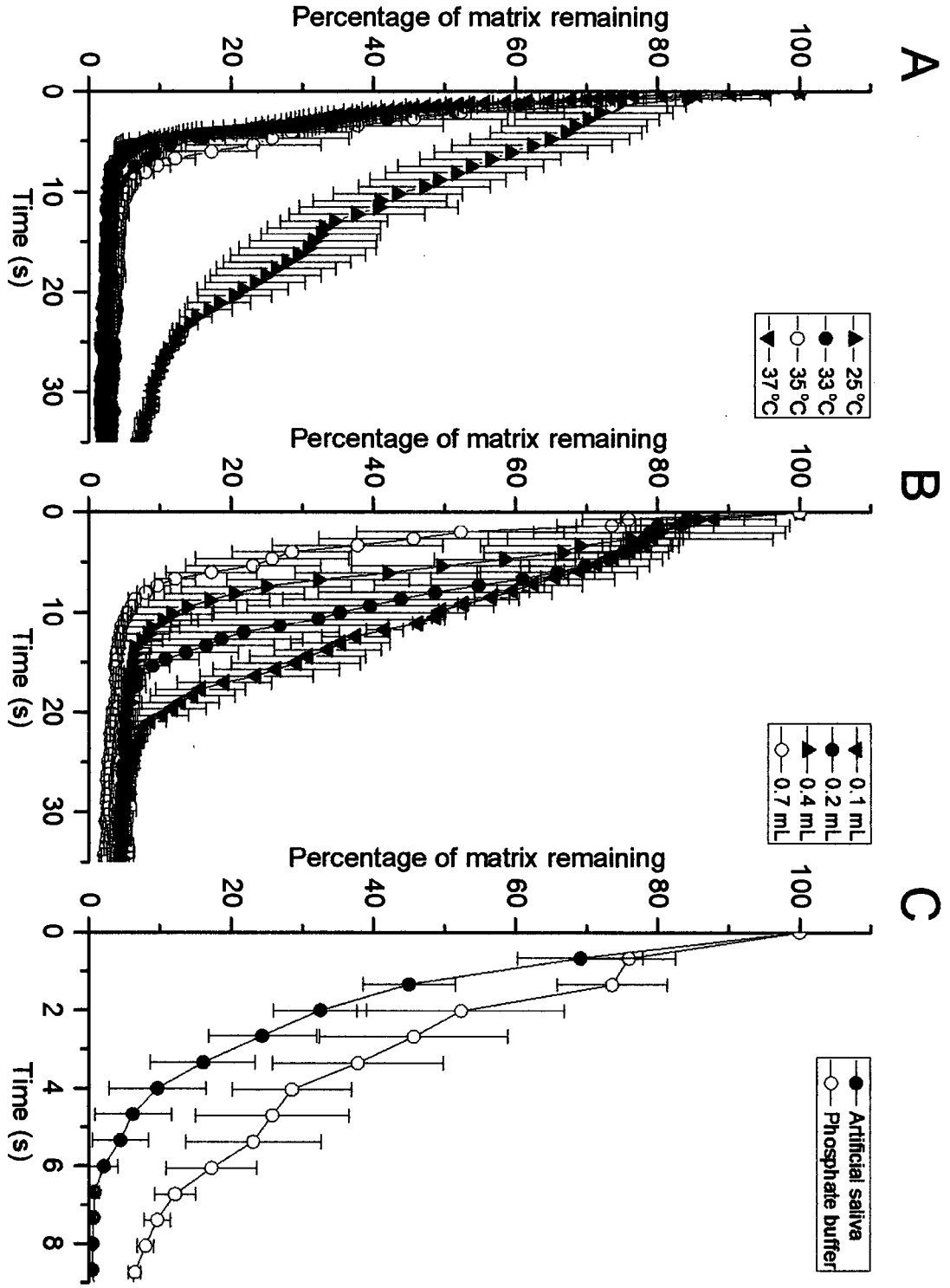
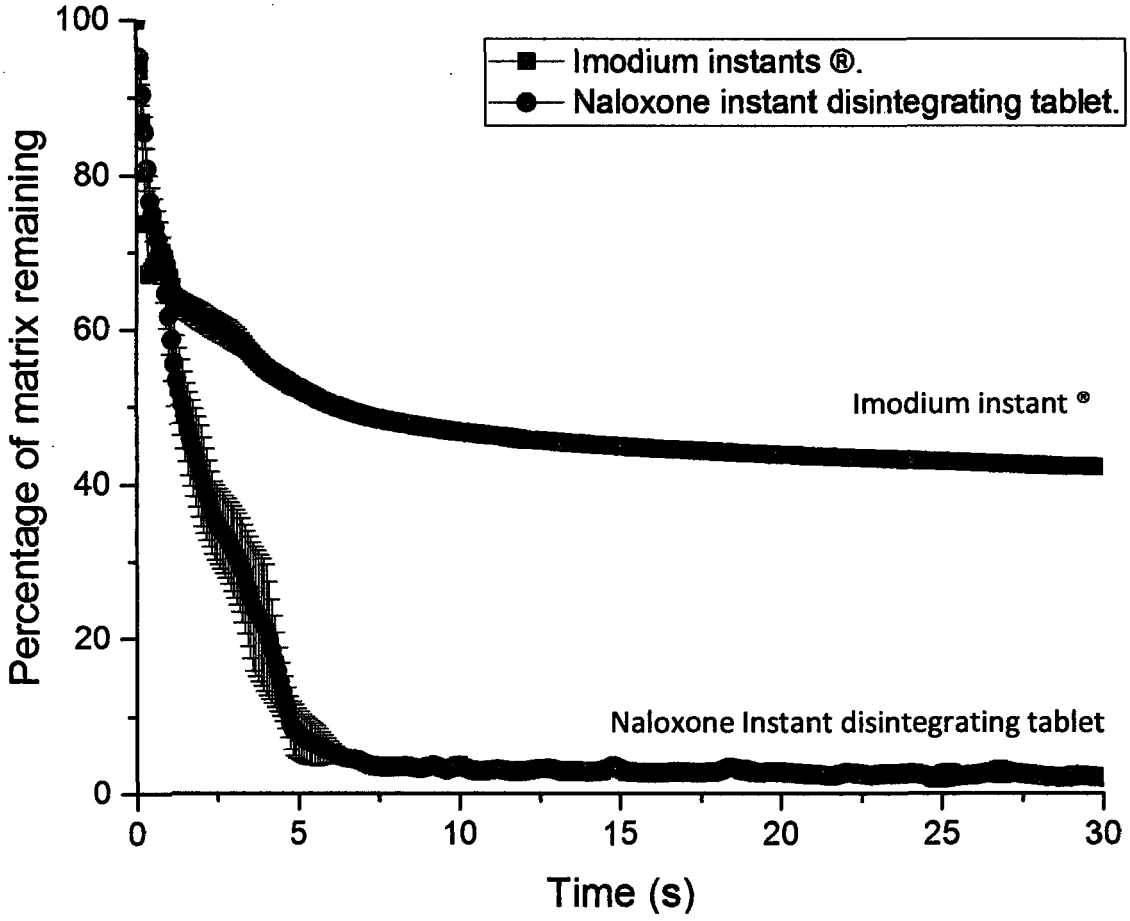

A
Percentage of matrix remaining
Time (s)
25 °C
33 °C
35 °C
37 °C
B
Percentage of matrix remaining
Time (s)
0.1 mL
0.2 mL
0.4 mL
0.7 mL
C
Percentage of matrix remaining
Time (s)
Artificial saliva
Phosphate buffer

Figure 8


Imodium instants ®.
Naloxone instant disintegrating tablet.
Percentage of matrix remaining
100
80
60
40
20
0
0
5
10
15
20
25
30
Time (s)
Imodium instant ®
Naloxone Instant disintegrating tablet

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2016/050682

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/00 A61K9/19 A61K9/20
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CN 1 813 740 A (YUE ZHENJIANG [CN]) 9 August 2006 (2006-08-09) cited in the application Background technology, Invention content examples 1-6 claims 1-3 -----	1-33
X	CN 102 000 037 A (BEIJING SHUANGLU LISHENG PHARMACEUTICAL CO LTD; BEIJING SHUANGLU PHARM) 6 April 2011 (2011-04-06) cited in the application Summary of the invention, Technical field, Background technology. examples 1, 2, 6 claims 1-5 ----- -/--	1-33

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 May 2016	09/06/2016

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	González Ferreiro, M

2

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CN 101 007 005 A (XUE JING [CN]) 1 August 2007 (2007-08-01) Background technology, Invention content examples 1-4 claims 1-3 -----	1-33
X	US 6 264 981 B1 (ZHANG HAO [US] ET AL) 24 July 2001 (2001-07-24) column 1 column 6 - column 9 table 1 claims 1, 13, 28, 30, 40, 49 -----	1-33

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2016/050682

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
CN 1813740 A	09-08-2006	NONE	
CN 102000037 A	06-04-2011	NONE	
CN 101007005 A	01-08-2007	NONE	
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		AU 1079701 A	08-05-2001
		CA 2388610 A1	03-05-2001
		EP 1242013 A1	25-09-2002
		ES 2345870 T3	05-10-2010
		HK 1050313 A1	10-09-2010
		JP 4815084 B2	16-11-2011
		JP 2003512402 A	02-04-2003
		JP 2008201805 A	04-09-2008
		MX PA02004235 A	21-04-2004
		PT 1242013 E	14-07-2010
		US 6264981 B1	24-07-2001
		WO 0130288 A1	03-05-2001